The opinion in support of the decision being entered today is not binding precedent of the Board.

Paper 1151

By: Trial Section Merits Panel
Board of Patent Appeals and Interferences
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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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GENCELL S.A.

Junior Party
U.S. Patent 6,127,175

v.

QING WANG, MITCHELL H. FINER and XIAO-CHI JIA

Junior Party,
Application 08/333,680

v.

GENCELL S.A.

Senior Party
Application 08/397,225

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Patent Interference No. 104,830 (CAS)

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Before: TORCZON, SPIEGEL and MILLS, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

**DECISION ON PRELIMINARY MOTIONS**

## I. Introduction

This is a decision following oral argument on the remaining preliminary and miscellaneous motions filed by parties Vigne/Gencell ('175), Wang ('680) and Perricaudet/Gencell ('225) in Interference 104,830. Steven B. Kelber, Esq., Linda Judge, Esq. and Sue Jensen, M.D., appeared for party Wang. James J. Maune, Esq. and Carmella L. Stephens, Ph.D. appeared for party Gencell.[1]

Interference 104,830 involves recombinant replication-defective[2] adenoviral vectors[3] wherein one or more essential functions[4] of at least[5] adenoviral early gene regions[6] E2 ("ΔE2") or E4 ("ΔE4") or both ("ΔE2ΔE4") are nonfunctional and

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[1] "Gencell" is used interchangeably with "Vigne/Gencell," Perricaudet/Gencell," "Vigne" and "Perricaudet in the decision because Gencell is the common assignee of both Vigne and Perricaudet.

[2] A replication-defective [or deficient] viral vector is a viral vector that is unable to replicate due to deficiencies in gene functions essential for replication (i.e., generation of viral progeny) to occur. Such viral vectors are able to replicate in complementing cell lines that provide the missing gene functions *in trans* or with the aid of a helper virus. [EX 1012] [Paper 39, "GENCELL S.A. SUBMISSION OF ADENOVIRUS MAPS AND GLOSSARY OF TERMS," hereinafter "Glossary," p. 8.]

[3] An adenoviral vector is an adenovirus that can carry a heterologous nucleic acid sequence (i.e., a transgene) into a suitable host cell. A transgene is a gene that is not normally present in a cell or viral vector, also called a heterologous or foreign gene. [Ex 1012] [Glossary, pp. 1 and 9.]

[4] An essential gene is a gene that codes for a function necessary for cell or viral viability or normal growth. Adenovirus essential gene functions are encoded by, e.g., the adenoviral early regions (e.g., the E1, E2 and E4 regions), late regions (e.g., the L1-L5 regions), genes involved in viral packaging, and virus-associated RNAs (e.g., VA-RNA I and/or VA-RNA-II). The E3 region is not required for adenoviral growth in culture. [Ex 1012] [Glossary, p. 3.]

[5] For simplicity, the expressions ΔE2, ΔE4 and ΔE2,ΔE4 as used herein are intended to encompass recombinant replication-defective adenoviruses and adenoviral vectors wherein the E3 region and/or essential functions of the E1 region are also non-functional, e.g., because a part or all of the region has been deleted.

[6] The early region is an area of the adenoviral genome that contains adenovirus genes expressed before the onset of viral DNA replication. The early region is divided into the E1A, E1B, E2A, E2B, E3 and E4 regions. [Ex 1012] [Glossary, p. 3.]

complementing cells[7] therefore.

Gencell has filed one miscellaneous and fifteen preliminary motions. Wang has filed one miscellaneous and four preliminary motions.

Gencell preliminary motion 1 sought (i) to substitute Count 1 with "Proposed Count 1," (ii) to cancel Perricaudet '225 claims 21, 22, 24 and 33, (iii) to amend Perricaudet '225 claims 1, 2 and 11, (iv) to add new claims 43-64 to Perricaudet '225 and (v) to obtain judgment that there is no interference-in-fact between the subject matter of Perricaudet '225 claim 35 and Wang '680 claim 46. Gencell preliminary motion 1 was dismissed. [Papers 101 and 103.]

The motions before us for consideration are:

1. Gencell preliminary motion 2 under 37 CFR § 1.633(b) seeks judgment of no interference-in-fact between the claims designated as corresponding to present Count 2. We grant this motion.

2. Contingent upon denial of Gencell preliminary motion 2, Gencell preliminary motion 3 under 37 CFR 1.633(c)(1) seeks to substitute "Proposed count 2" for present Count 2 and Gencell preliminary motion 8 seeks to substitute "Proposed count 6" for present Count 6. These motions are dismissed.

3. Gencell preliminary motion 4 under 37 CFR § 1.633(c)(1) seeks to substitute "Proposed count 3" for present Count 3. We deny this motion.

4. Gencell preliminary motions 5 and 6 under 37 CFR § 1.633(b) seek

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[7] A complementing cell is a cell that enables growth of viral vectors deficient in gene functions essential for growth by providing the missing gene function(s) *in trans*. The 293 cell line, for example, is a permanent cell line of primary human embryonal kidney cells transformed by sheared human adenovirus type 5 (Ad 5) DNA that expresses the adenoviral E1A and E1B genes. [Ex 1012] [Glossary, pp. 1 and 2.]

judgments of no interference-in-fact between the claims designated as corresponding to Counts 4 and 6, respectively. These motions are denied.

5. Contingent upon the denial of preliminary motion 6, Gencell preliminary motion 9 seeks to substitute "Proposed count 4" for present Count 4. We deny this motion.

6. Gencell preliminary motion 7 under 37 CFR § 1.633(c)(1) seeks to substitute "Proposed count 5" for present Count 5. We grant this motion, without prejudice to the APJ taking further appropriate action.

7. Gencell preliminary motions 10-15 seek benefit for the purpose of priority of the filing dates of FR 93/08596 (July 13, 1993); FR 94/04590 (April 18, 1994) and PCT/FR94/00851 (July 8, 1994), as to "Proposed counts 1-6", respectively. We dismiss Gencell preliminary motions 10-13 and 15. We deny Gencell preliminary motion 14.

8. Gencell miscellaneous motion 2 seeks to suppress Exhibit 2022, the Ketner deposition transcript. We dismiss this motion.

9. Wang preliminary motion 1, seeks a judgment of no interference-in-fact between any of the involved Wang claims and any of the involved Perricaudet claims.

As to Count 1, we find no interference-in-fact between Wang claims 46 and 56 and Perricaudet claims 1-3, 9, 12-18, 28, 30, 35 and 40-41.

As to Count 2, we find no interference-in-fact between Wang claim 48 and Perricaudet claims 19-20, 23 and 25-27.

As to Count 3, we find no interference-in-fact between Wang claims 37-38, 46-47, 52, 54 and 56 and Perricaudet claims 1-3, 9, 12-18, 28, 30 and 40-41, as currently

amended, but find an interference-in-fact between Wang claims 37-38, 46-47, 52, 54 and 56 and Perricaudet claim 34 and Vigne claim 33.

As to Count 4, we find no interference-in-fact between Wang claims 39-44 and 57 and Perricaudet claims 19-23, 25, 27 and 33, but find an interference-in-fact between Wang claims 39-44 and Vigne claims 1-6, 11-16, 20-21 and 23-25.

As to Count 5, we find an interference-in-fact between Wang claims 37, 46, 54 and 56 and Perricaudet claim 42.

As to Count 6, we find no interference-in-fact between Wang claims 48 and 57 and Perricaudet claim 24.

10. Wang preliminary motion 2 seeks judgment against Vigne pursuant to Rule 602(a)(2) because the involved Vigne patent and the involved Perricaudet application are owned by a single party, Gencell. This motion is dismissed without prejudice to the APJ taking further appropriate action.

11. Wang preliminary motion 3 seeks judgment that Perricaudet claims 1-3, 9, 12-28, 30, 33-35 and 40-42 are unpatentable under 35 U.S.C. § 112, first paragraph, as allegedly not enabled throughout their scope. We grant this motion with respect to claim 34 and 42. We dismiss this motion with respect to the remaining claims.

12. Wang preliminary motion 4 seeks judgment that Perricaudet claim 42 is unpatentable under 35 U.S.C. § 112, first paragraph, as allegedly not adequately described in the '225 specification. We grant this motion.

## II. Findings of fact (FF)

The following findings of fact are supported by a preponderance of the evidence.

### A. Junior party Vigne/Gencell

1. Junior party, Emmanuelle Vigne, Michel Perricaudet, Jean-François Dedieu, Cécile Orsini, Patrice Yeh, Martine Latta and Edouard Prost (**Vigne/Gencell**), is involved in the interference on the basis of U.S. Patent 6,127,175 ("Vigne '175"), issued October 3, 2000, based on U.S. application 08/875,223 ("Vigne '223"), filed July 17, 1997.

2. Vigne '175 has been accorded benefit for the purpose of priority of

(i) PCT application PCT/FR96/00088, filed January 19, 1996, ("Vigne PCT")

(ii) FR application 95/10541, filed September 8, 1995 ("Vigne '541"),

(iii) FR application 95/06532, filed June 1, 1995 ("Vigne '532") and

(iv) FR application 95/00747, filed January 20, 1995 ("Vigne '747").

3. Vigne '175 is assigned to Gencell S.A.

### B. Junior party Wang

4. Junior party, Qing Wang, Mitchell H. Finer and Xiao-Chi Jia (**Wang**) is involved in the interference on the basis of U.S. application 08/333,680 ("Wang '680"), filed November 3, 1994.

5. Wang '680 is assigned to Cell Genesys, Inc.

### C. Senior party Perricaudet/Gencell

6. Senior party, Michel Perricaudet, Emmanuelle Vigne and Patrice Yeh (**Perricaudet/Gencell**), is involved in the interference on the basis of U.S. application

08/397,225 ("Perricaudet '225"), filed March 28, 1995.

7. Perricaudet '225 has been accorded benefit for the purpose of priority of

(i) PCT application PCT/FR94/00851, filed July 8, 1994 ("Perricaudet PCT"),

(ii) FR application 94/04590, filed April 18, 1994 ("Perricaudet '590") and

(iii) FR application 93/08596, filed July 13, 1993 ("Perricaudet '596").

8. Perricaudet '225 is assigned to Gencell S.A.

9. Perricaudet claims 1, 2 and 11 were amended subsequent to the declaration of this interference in accordance with the MEMORANDUM OPINION and ORDER (Paper No. 64) filed in related interference 104,824 (see Paper 102 herein).

**D. Counts and claims of the parties**

10. The interference is defined by six (6) counts. Counts 1, 3 and 5 are directed to recombinant adenoviral vectors unable to replicate due to deficiencies in essential gene functions of the (a) E2, (b) E4 and both (c) E2 and E4 regions, respectively. Counts 2, 4 and 6 are directed to corresponding complementing cell lines therefore.

11. **Count 1** is defined by Wang claim 46, wherein the two gene regions are E1 and E2A, or Perricaudet claim 35.

12. Wang claim 46 reads:

> 46. A recombinant adenoviral vector, wherein said vector comprises at least a lethal deletion or mutation in two gene regions selected from the group consisting of E1, E2A and E4 early gene regions; and additionally comprises a transgene so that when rescued the resulting recombinant adenovirus requires for replication at most complementation of genes of the E1, E2A and E4 adenoviral early gene regions.

13. Perricaudet claim 35 reads:

35. A replication defective recombinant adenovirus comprising
ITR sequences,
an encapsulation sequence,
a heterologous DNA sequence, and
an E4 region,
wherein the E4 region is the sole adenoviral region.

14. **Count 2** is defined by Wang claim 48, wherein the two gene regions are E1 and E2A, or Perricaudet claim 26.

15. Wang claim 48 reads:

48. A packaging cell line derived from a 293-cell that supplies the function of the E2A and E4 early gene regions wherein the nucleotide sequences encoding the E2A and E4 early gene regions are operably linked to an inducible promoter and that supports the growth of a mutant adenovirus defective in replication, wherein said adenovirus comprises at least a lethal deletion or mutation in two gene regions selected from the group consisting of E1, E2A and E4 early gene regions; and so that when rescued the resulting recombinant adenovirus requires for replication complementation of genes of the E1, E2A and E4 early gene region.

16. Perricaudet claim 26 depends on claims 19 and 1 (now amended) and reads:

26. The cell line according to claim 19

[19. A cell line comprising, integrated into its genome, adenovirus genes necessary to complement the replication defective recombinant adenovirus according to claim 1

[1. A replication defective recombinant adenovirus comprising
ITR sequences,
an encapsulation sequence and
a heterologous DNA sequence,

wherein E1 genes have been rendered non-functional by deletion, and wherein E2 genes, but not E4 genes, have been rendered non-functional by deletion],

wherein one of the complementing genes is under the control of an inducible promoter],

comprising a gene encoding the 72 K protein of E2, wherein the 72 K protein encoding gene is placed under the control of an inducible promoter.

17. **Count 3** is defined by Vigne claim 33 or Wang claim 37 or Perricaudet claim 34.

18. Vigne claim 33 reads:

33. A defective recombinant adenovirus ΔE1,ΔE4, wherein all or part of the E1 region and the whole of the E4 region, chosen from the group consisting of Ad5 nucleotides 33466-35355 and 33093-35355, or the corresponding nucleotides from Ad2, Ad7 or Ad12, are deleted.

19. Wang claim 37 reads:

37. A replication-defective recombinant adenovirus, wherein the genome of said adenovirus contains at least two lethal deletions, two lethal mutations, or one lethal deletion and one lethal mutation in the E1 and E4 early gene regions, so that the recombinant adenovirus requires for replication at most complementation of genes of the E1, E2A and E4 adenoviral early gene regions, wherein said recombinant adenovirus genome additionally contains a transgene.

20. Perricaudet claim 34 reads:

34. A replication defective recombinant adenovirus comprising
ITR sequences,
an encapsulation sequence,
a heterologous DNA sequence, and an E2 region,
wherein the E2 region is the sole adenoviral early region.

21. **Count 4** is defined by Vigne claim 1 or Wang claim 39 or Perricaudet claim 22.

22. Vigne claim 1 reads:

1. A recombinant cell line for the production of a defective adenovirus comprising, inserted into its genome, part of an adenovirus E4 region comprising on ORF6 reading frame under the control of a functional promoter, wherein the inserted E4 region does not contain a functional ORF4 reading frame.

23. Wang claim 39 reads:

39. A packaging cell line derived from a 293 cell that supports the growth of a replication defective recombinant adenovirus that carries at least a lethal deletion in each of adenovirus E1 and E4 early gene regions, so that the recombinant adenovirus requires for replication complementation of genes of both the E1 and E4 adenoviral early gene regions, comprising a cell line that supplies the function of the E1 early gene region and the E4 early gene region wherein nucleotide sequences encoding the E4 early gene region is operably linked to an inducible promoter.

24. Perricaudet claim 22 depends on claims 19 and 1 (now amended) and reads:

22. The cell line according to claim 19,

[19. A cell line comprising, integrated into its genome, adenovirus genes necessary to complement the replication defective recombinant adenovirus according to claim 1

[1. A replication defective recombinant adenovirus comprising
ITR sequences,
an encapsulation sequence and
a heterologous DNA sequence,
wherein E1 genes have been rendered non-functional by deletion, and wherein E2 genes, but not E4 genes, have been rendered non-functional by deletion],

wherein one of the complementing genes is under the control of an inducible promoter],

wherein it comprises, in its genome, an E1 gene and an E4 gene wherein

the E4 gene is under the control of an inducible promoter.

25. **Count 5** is defined by Wang claim 46, wherein the two gene regions are E1 and E4, or Perricaudet claim 42.

Wang claim 46 is reproduced at FF 12 above.

26. Perricaudet claim 42 reads:

> 42. A replication-defective adenovirus comprising an adenoviral genome that requires, for replication, complementation *in trans* of an essential gene function in each of at least two or more adenoviral early regions selected from the group consisting of the E1, E2A, and E4 regions of an adenoviral genome, wherein the adenovirus comprises one or more functional early or late gene regions of an adenoviral genome and requires complementation of an essential gene function in each of at least the E2A and E4 regions, wherein the adenovirus comprises a heterologous DNA sequence.

27. **Count 6** is defined by Wang claim 48 or Perricaudet claim 24.

Wang claim 48 is reproduced at FF 15 above.

28. Perricaudet claim 24 depends on claims 19 and 1 (now amended) and reads:

> 24. The cell line according to claim 19,
>
> [19. A cell line comprising, integrated into its genome, adenovirus genes necessary to complement the replication defective recombinant adenovirus according to claim 1
>
> [1. A replication defective recombinant adenovirus comprising
> ITR sequences,
> an encapsulation sequence and
> a heterologous DNA sequence,
> wherein E1 genes have been rendered non-functional by deletion, and wherein E2 genes, but not E4 genes, have been rendered non-functional by deletion],

wherein one of the complementing genes is under the control of an inducible promoter],

wherein it comprises E2 and E4 genes and the E2 and E4 genes are under the control of an inducible promoter.

29. The claims of the parties are:

| | |
|---|---|
| Wang | 37-48, 52, 54, 56-57 |
| Vigne | 1-33 |
| Perricaudet | 1-3, 6, 9-30, 33-42 |

30. The claims of the parties which correspond to Count 1 are:

| | |
|---|---|
| Wang | 46, 56 |
| Vigne | None |
| Perricaudet | 1-3, 9, 12-18, 28, 30, 35, 40-41 |

31. The claims of the parties which correspond to Count 2 are:

| | |
|---|---|
| Wang | 48 |
| Vigne | None |
| Perricaudet | 19-20, 23, 25-27 |

32. The claims of the parties which correspond to Count 3 are:

| | |
|---|---|
| Wang | 37-38, 46-47, 52, 54, 56 |
| Vigne | 33 |
| Perricaudet | 1-3, 9, 12-18, 28, 30, 34, 40-41 |

33. The claims of the parties which correspond to Count 4 are:

| | |
|---|---|
| Wang | 39-44, 57 |
| Vigne | 1-6, 11-16, 20-21, 23-25 |
| Perricaudet | 19-23, 25, 27, 33 |

34. The claims of the parties which correspond to Count 5 are:

| | |
|---|---|
| Wang | 37, 46, 54, 56 |
| Vigne | None |
| Perricaudet | 42 |

35. The claims of the parties which correspond to Count 6 are:

| | |
|---|---|
| Wang | 48, 57 |
| Vigne | None |
| Perricaudet | 24 |

36. The claims of the parties which do not correspond to any of Counts 1 through 6, and therefore are not involved in the interference, are:

| | |
|---|---|
| Wang | 45 |
| Vigne | 7-10, 17-19, 22, 26-32 |
| Perricaudet | 6, 10-11, 29, 36-39 |

Other findings of fact follow below.

## III. GENCELL PRELIMINARY MOTION 2

Gencell moves pursuant to 37 CFR § 1.633(b) for judgment of no interference-in-fact between the claims designated as corresponding to Count 2, i.e., Wang claim 48 and Perricaudet claims 19-20, 23 and 25-27 (Paper 41). Wang opposes (Paper 64); Gencell replies (Paper 85).

Prior to analysis of Gencell preliminary motion 2, we address the scope of Perricaudet claim 26.

Perricaudet claim 26 is repeated below (emphasis added).

26. The cell line according to claim 19

> [19. A cell line comprising, integrated into its genome, adenovirus genes necessary to complement the replication defective recombinant adenovirus according to claim 1
>
> > [1. A replication defective recombinant adenovirus comprising
> > ITR sequences,
> > an encapsulation sequence and
> > a heterologous DNA sequence,
> > wherein E1 genes have been rendered non-

functional by deletion, and **wherein E2 genes, but not E4 genes,** have been rendered non-functional by deletion],

wherein one of the complementing genes is under the control of an inducible promoter],

comprising a gene encoding the 72 K protein of E2, wherein the 72 K protein encoding gene is placed under the control of an inducible promoter.

Perricaudet claim 26 requires that the claimed cell line complements for multiple E2 gene deletions, expressly including deletion of the E2A gene region encoding the 72 kD protein. Thus, the claim encompasses complementing for deletions of both the E2A and E2B gene regions.

In Gencell preliminary motion 2, Gencell moves for judgment of no interference-in-fact as to the subject matter of Count 2. Gencell contends there are three patentable distinctions between Perricaudet claim 26 and Wang claim 48. According to Gencell, Wang claim 48 requires genes from both E2A and E4 to be present in its complementing cell line whereas the claimed Perricaudet complementing cell line does not require the presence of E4. Further according to Gencell, Perricaudet claim 26 requires the gene encoding the 72 kD protein to be integrated into the cell's genome and under the control of an inducible promoter. [Paper 41, pages 5-6.].

If party A establishes that its claims do not interfere with the claims of its opponent B, because the subject matter of A's claims neither anticipates nor renders obvious the subject matter of B's claims even if it is assumed that A made its invention first, the claims of A are not an impediment to granting a patent to B. Cf. Case v. CPC International, Inc., 730 F.2d 745, 749, 221 USPQ 196, 200 (Fed. Cir. 1984) (no

interference-in-fact means that there is no interfering subject matter and that Case's patent is no impediment to granting CPC the claims of its application).

Thus, Gencell can establish that no interference-in-fact exists by showing that none of the involved Perricaudet claims corresponding to each respective Count is anticipated or rendered obvious by any of the involved Wang claims corresponding to each said respective Count or vice versa. That is, no interference-in-fact is subject to a "one-way" test for patentable distinctiveness.

In addition, a party filing a motion has the burden to show that it is entitled to the relief requested by a preponderance of the evidence. Kubota v. Shibuya, 999 F.2d 517, 522, 27 USPQ2d 1418, 1422-1423 (Fed. Cir. 1993). 37 CFR § 1.637(a), first sentence; Bruning v. Hirose, 161 F.3d 681, 684, 48 USPQ2d 1934, 1937 (Fed. Cir. 1998) (burden of proof on the issue of patentability of the claims of a patent in an interference where applications are copending is by a preponderance of the evidence); Winter, 53 USPQ2d at 1244.

**A. A cell line supplying the function of both E2 and E4 is patentably distinct from a cell line supplying E2A function but not E4 function.**

According to Gencell, the E2 gene region encodes three proteins, i.e., adenoviral DNA polymerase, preterminal protein and DNA binding protein (Paper 41, p. 7). Each of these proteins is involved in adenoviral replication. In contrast, Gencell states that "the expressed proteins from the E4 region contribute to a range of functions including viral growth, viral DNA replication, late mRNA synthesis, induction of host cell protein synthesis shutoff and viral particle assembly [EX 1017, EX 1018][8]" (id.). Gencell

[8] Gencell expressly refers to Exs 1017 and 1018 in its motion, but fails to cite to either of these documents in the "EVIDENCE RELIED UPON IN SUPPORT OF THIS MOTION" portion of its motion

argues that the proteins encoded by E2 and E4 "perform distinct functions which are not interchangeable" (id., p. 7). Gencell contends that deletion of a protein involved in replication (i.e., one encoded by E2) does not teach, suggest, or provide motivation for deletion of a protein responsible for splicing of viral mRNAs (i.e., one encoded by E4) (id.). Thus, Gencell submits that "it would not have been obvious to render the E2 genes nonfunctional by deletion, given a replication defective adenovirus comprising E4 genes which have been rendered non-functional by deletion. Nor would it not [sic] be obvious to render the E4 genes nonfunctional by deletion, given a replication defective adenovirus comprising E2 genes which have been rendered non-functional by deletion" (id., pp. 7-8).

As noted above, Wang claim 48 requires the recited cell line to supply the functions of both E2A and E4 genes, whereas now, subsequent to the amendment of Perricaudet claim 1, the cell line recited in Perricaudet claim 26 is not required to supply the E4 gene function. Therefore, neither cell line now anticipates the other because one requires supplying the E4 function whereas the other does not.

Moreover, Perricaudet claim 26 seems to teach away from a cell line supplying the E4 function by virtue of supporting replication of a vector which must have E4 present. In other words, on its face, it would not appear obvious to modify the Perricaudet cell line by supplying E4 gene function to a vector that already possesses E4 gene function, but not E2 function, because E2 and E4 encode different proteins which do not function interchangeably. We find this argument persuasive when taken

paper (Paper 41, p. 2). Moreover, Gencell fails to provide a specific citation to either document in its motion. Regardless, in this particular circumstance we exercise our discretion and consider Exs 1017 and 1018.

in light of the supporting evidence referenced by Gencell. We note that Wang does not oppose this argument.[9] However, we do not find Gencell's remaining two arguments persuasive for the following reasons.

**B. Simply pointing to differences between cells carrying heterologous DNA integrated into their genome vis-a-vis episomally transfected cells is insufficient to establish nonobviousness between Perricaudet's "species" claim and Wang's "genus" claim.**

Gencell also argues that cells having heterologous DNA integrated into their genome are patentably distinct from cells having heterologous DNA carried on extrachromosomal episomes (Paper 41, page 9). In support of this position, Gencell cites Kaufman[10] [EX 1015, pp. 495-496] for the proposition that transfection efficiency varies tremendously and often less than one in ten treated cells acquire heterologous DNA supplied via episomes.

Gencell generally discusses expected differences between what happens when a cell takes up heterologous DNA (i.e., is transfected) and either physically incorporates that DNA into its genome (i.e., "stably transfected") or not (i.e., "transiently transfected"). For example, heterologous DNA that is not incorporated into the cell's genome is present as an "extrachromosomal element", e.g., a plasmid. As one might expect, and Gencell argues, DNA that is not incorporated into the cell's genome will eventually be lost over time, while DNA that is incorporated into the cell's genome

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[9] Wang has not argued in its opposition that supplying E2 or E4 function is equivalent for obtaining adenoviral vector growth. Rather, Wang's position is that "cell lines wherein the complementing genes are stably integrated into the genome are a distinct species within the broader genus of Wang's claims." [Paper No. 64, p.1].

[10] Randal J. Kaufman, "Vectors Used for Expression in Mammalian Cells," Chapter 39 in METHODS IN ENZYMOLOGY, Vol. 185, Gene Expression Technology, David V. Goeddel, ed., Academic Press, Inc., San Diego (1990), pp. 487-511 (Ex 1015).

becomes a part of the cell, i.e., the cell line becomes "clonal". Gencell again cites to Kaufman (Ex 1015).

37. According to Kaufman,

> With most methods of DNA transfer, 5-50% of the cells in the population acquire DNA and express it transiently over a period of several days to several weeks. Eventually, the DNA is lost from the population. This transient expression of transfected DNA is conveniently used instead of the more laborious procedure of isolating and characterizing stably transfected cell lines. Transient expression experiments obviate the effects of integration sites on expression and the possibility of selecting cells which harbor mutations in the transfected DNA. Transient expression offers convenient means by which to compare different vectors and identify that an expression plasmid is functional **before establishing stable cell lines**. The efficiency of expression from transient transfection is dependent on the number of cells which take up the transfected DNA, the gene copy number, and the expression level of the gene. ... [Ex 1015, p. 495, ¶ 2, emphasis added.]
>
> * * * * * *
>
> ... Today, most useful vectors contain multiple elements which include (1) an SV40 origin of replication for amplification to high copy number in COS monkey cells, (2) an efficient promoter element for transcription initiation, (3) mRNA processing signals which include mRNA cleavage and polyadenylation sequences and frequently also intervening sequences, (4) polylinkers that contain multiple endonuclease restriction sites for insertion of foreign DNA, and (5) **selectable markers that can be used to select cells that have stably integrated the plasmid DNA**. [Id., p. 496, ¶ 1, emphasis added.]
>
> * * * * * *
>
> ... The level of protein expression from heterologous genes introduced into mammalian cells depends on multiple factors, including DNA copy number, efficiency of transcription, mRNA processing, transport, stability, and translational efficiency, and protein processing, secretion, and stability. The rate-limiting step for high-level expression may be different for different genes. [Id., ¶ 2.]

A fair reading of Kaufman (Ex 1015, pp. 495-496), however, suggests that one of ordinary skill in the art would have had a number of motivations to construct episomally transfected cells, including as a precursor to constructing cells having heterologous DNA integrated into their genome. Moreover, to the extent Gencell seems to argue that

> "[e]pisomes carrying large heterologous gene fragments may be particularly susceptible to failed, inadequate expression or loss of the episome. [EX 1015 at pp. 487-512.]",

Gencell (a) fails to provide any specific citation to Kaufman (Ex 1015), (b) fails to define a "large" gene fragment or how it relates to the claims at issue, and (c) fails to explain how this apparently expected result relates to the obviousness question at hand.

If anything, Kaufman (Ex 1015) suggests that cell transfection, both transient and stable, is well within ordinary skill in the art;[11] and, recognized as useful for known, defined purposes, e.g., to identify that an expression plasmid is functional ("transient") before establishing stable cell lines to analyze gene function ("stable").

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[11] See also, "unit 9.5" contributed by Mortensen et al., "Selection of Transfected Mammalian Cells," in CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, Vol. 2, Ausubel et al. eds., John Wiley & Sons, Inc., (1994-1998), pp. 9.5.1-9.5.19 (Ex 1013, hereinafter "Ausubel").

Ausubel (Ex 1013), appears to be a how-to manual for constructing stably transfected cells. The opening paragraph in Ausubel reads

> Analysis of gene function frequently requires the formation of mammalian cell lines that contain the studied gene in a stably integrated form (*UNIT 16.12*). Approximately one in $10^4$ cells in a transfection will stably integrate DNA (the efficiency can vary depending on the cell type). Therefore, a dominant, selectable marker is used to permit isolation of stable transfectants. In the first part of this unit, the procedure for determining selection conditions and the resulting stable transfection is presented (see Basic Protocol 1) and the most commonly used selectable markers are discussed (see Basic Protocol 2). Basic Protocol 2 includes conditions for thirteen markers commonly used for selection of mammalian cells.

Simply pointing to the differences between the two types of transfection is insufficient to establish that a stable transfection is an unobvious species of transfection. Moreover, expected results are not evidence of unobviousness. For example, stably transfected cells having heterologous DNA physically incorporated into their genome would be expected to be "clonal", whereas transiently transfected cells would not. Nor has Gencell advanced any evidence or reasoned argument that various "challenges" encountered in cell transfection are outside of ordinary skill. Therefore, this argument fails on both procedural and substantive grounds. Gencell has not established by a preponderance of the evidence that one of ordinary skill in the art (a) would not have been aware of the relative advantages and disadvantages of transient (episomal) transfection versus stable (chromosomally integrated) transfection of cells with heterologous DNA, (b) would not have been aware of appropriate uses of a transiently transfected cell (e.g., to identify expression plasmids that are functional and, therefore, useful in establishing stable cell lines) versus a stably transfected cell (e.g., to analyze gene function), or (c) would not have been able to obtain and select for either stably transfected cells or transiently (episomally) transfected cell lines, as desired, without undue experimentation at the time of the invention.

Insofar as Gencell relies on vague citations, e.g., EX 1015, pp. 487-512, to support its arguments (Paper 41, pp. 10), its motion is also procedurally defective. As stated in Section 26(a) of the STANDING ORDER

> Citation to the evidence must be specific, i.e., (1) by column and line of a patent, (2) page, column and paragraph of a journal article and (3) page and line of a cross-examination deposition transcript. Citations to an entire document or numerous pages of a cross-examination

> deposition transcript do not comply with the requirement for a citation to the record. In this respect, the Trial Section adopts as its policy the rationale of Clintec Nutrition Co. v. Baxa Corp., 44 USPQ2d 1719, 1723 n.16 (N.D. Ill. 1997), which notes that where a party points the court to multi-page exhibits without citing a specific portion or page, the court will not pour over the documents to extract the relevant information, citing United States v. Dunkel, 927 F.2d 955, 956 (7th Cir. 1991). Nor will the board take on the role of an advocate for one of the parties. Compare Ernst Haas Studio, Inc. v. Palm Press, Inc., 164 F.3d 110, 111-12, 49 USPQ2d 1377, 1378-79 (2d Cir. 1999).

We decline to shift through Gencell's general citations to glean where they might support specific points relevant to Gencell's arguments. A party filing a motion has the burden of proof and must establish its right to any substantive relief requested in the motion. 37 CFR § 1.637(a). See Hillman v. Shyamala, 55 USPQ2d 1220, 1221-22 (Bd. Pat. App. & Int. 2000).

Therefore, this argument fails on both procedural and substantive grounds for the reasons set forth above.

**C. Cell lines transfected with genes driven by promoters are preferred when the genes encode a cytotoxic protein.**

Gencell references Ex 1004 as supporting the proposition that the E4 gene expresses six toxic proteins (Paper 41, p. 8). Again, Gencell does not point out, and we do not find, where Ex 1004 provides such support.

Gencell also references Ex 1004 as supporting the proposition that "mutations may spontaneously arise in the transgene, which may be undesirable for use in a given experimental context" (Paper 41, p. 10). Gencell not only fails to provide a specific citation to Ex 1004 in support of its statement (see STANDING ORDER, § 26(a)), but also fails to explain how "a given experimental context" relates to the subject matter of

Count 2 (37 CFR § 1.637(a)).

Gencell relies on Ex 1013, pp. 9.5.1-9.5.19 (Paper 41, ¶ bridging pp. 10-11) to support its position that identifying and isolating successful integrations of genes encoding toxic proteins into cellular genomes can be problematic. Gencell again fails to provide a specific citation to Ex 1013 in support of its, appears to be arguing enablement rather than obviousness, and relies on a document which it failed to cite in the "EVIDENCE RELIED UPON IN SUPPORT OF THIS MOTION" portion of its motion paper (Paper 41, p. 2). Nonetheless, we note a subsection entitled "Inducible Promoters" on page 497 of Kaufman (Ex 1015). The subsection begins with "[i]n order to express a protein which is potentially cytotoxic, it is advisable to use an inducible expression system which is regulated by external stimulus" (id., p. 497, ¶ 2). Thus, Kaufman (Ex 1015) would have motivated one of ordinary skill in the art to use an inducible promoter when constructing a complementing cell line expressing a cytotoxic protein as well as a reasonable expectation of success. Therefore, this argument is not persuasive.

In summary, we find argument (A) persuasive but not argument (B) or (C) for the reasons given above. Gencell preliminary motion 2 is **granted.**

## IV. GENCELL PRELIMINARY MOTION 3

Contingent upon the denial of Gencell preliminary motion 2, Gencell moves pursuant to 37 CFR § 1.633(c)(1) to substitute "Proposed count 2" for present Count 2, to cancel Perricaudet claims 21, 22, 24 and 33, to amend Perricaudet claims 1, 2 and 11, and to add new Perricaudet claims 43-64 (Paper 42). Wang opposes (Paper 65);

Gencell replies (Paper 77).

Gencell preliminary motion 3 is moot in view of the granting of Gencell preliminary motion 2.

Therefore, Gencell preliminary motion 3 is **dismissed** as moot.

## V. GENCELL PRELIMINARY MOTION 8

Contingent on the denial of Gencell preliminary motion 2, Gencell moves pursuant to 37 CFR § 1.633(c)(1) to substitute Gencell's "Proposed count 6" for present Count 6 and to designate Wang claims 48 and 57 and proposed new Perricaudet claim 64 as corresponding to "Proposed Count 6" (Paper 47). Wang opposes (Paper 69); Gencell replies (Paper 79).

Gencell preliminary motion 8 is moot in view of the granting of Gencell preliminary motion 2.

Therefore, Gencell preliminary motion 8 is **dismissed** as moot.

## VI. GENCELL PRELIMINARY MOTION 5

Gencell moves pursuant to 37 CFR § 1.633(b) for judgment of no interference-in-fact between the claims of Wang and Gencell/Vigne corresponding to Count 4, i.e., Wang claims 39-44 and 57 and Vigne claims 1-6, 11-16, 20-21 and 23-25 (Paper 44). Wang opposes (Paper 67); Gencell replies (Paper 86).

As stated above, Count 4 is alternatively defined by Vigne claim 1 or Wang claim 39 or Perricaudet claim 22 (FF 21).

Wang claim 39 is directed to a packaging cell line derived from a 293 cell that supports the growth of a replication defective recombinant adenovirus that carries at

least a lethal deletion in each of adenovirus E1 and E4 early gene regions, so that the recombinant adenovirus requires for replication complementation of genes of both the E1 and E4 adenoviral early gene regions, comprising a cell line that supplies the function of the E1 early gene region and the E4 early gene region wherein nucleotide sequences encoding the E4 early gene region is operably linked to an inducible promoter (FF 23).

Vigne claim 1 is directed to a complementing cell line comprising part of an E4 gene region comprising an open reading frame 6 ("ORF6") under the control of a functional promoter, but not containing a functional ORF4 integrated into its cellular genome (FF 22).

Gencell argues (Paper 44, p. 6, ll. 9-16) that

> [c]laim 39 of Wang '680 encompasses cell lines that contain at least one E4 gene, however, in contrast to claim 1 of Vigne '175, the cells embraced by Claim 39 of Wang '680 do not require expression of E4 ORF6, and are not limited to cells that lack the E4 ORF4 reading frame.
>
> In addition, Claim 1 of Vigne '175 encompasses recombinant cell lines having an adenovirus E4 region, comprising and ORF6 reading frame, inserted into the genome. In contrast, the cells embraced by Wang '680 do not require that the adenoviral genes be integrated into the genome." [Paper 44, page 6, ll. 9-16.]

**A. Gencell preliminary motion 5 is procedurally defective.**

Gencell once again fails to provide specific citation to the evidence relied on in support of its motion. Compare Paper 44, pp. 8-9 to STANDING ORDER, § 26(a).

**B. The essential E4 sequences required for virus replication may reside solely within the amino terminus of ORF6.**

Secondly, according to Cutt (Ex 2021,[12] p. 550, c. 2, last ¶), "the essential E4 sequences required for virus viability in lytic infection may reside solely within the amino terminus of ORF6." Thus, it would have been obvious to one of ordinary skill in the art at the time of the present invention, in view of Cutt (Ex 2021), to provide essential E4 function with a complementing cell line containing only that part of E4 encoding its amino terminus, i.e., ORF6, because E4 ORF6 supplies the E4 function required for viral replication, thereby avoiding expression of potentially toxic proteins encoded by other E4 ORFs.

Moreover, we find Gencell's argument regarding the non-obviousness of deleting all but E4 ORF6 of the adenovirus to be unsupported by evidence of record. (Paper 44, pp. 9-10). The argument presented by Gencell is attorney argument and does not constitute evidence. Attorney argument cannot take the place of evidence lacking in the record. Meitzner v. Mindick, 549 F.2d 775, 782, 193 USPQ 17, 22 (CCPA), cert. denied, 434 U.S. 854 (1977). In re DeBlauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984), In re Payne, 606 F.2d 303, 315, 203 USPQ 245, 256 (CCPA 1979). Unsupported speculation, absent evidence, is insufficient to establish that Gencell is entitled to the relief requested in its motion. Again, Gencell has not satisfied its initial burden of providing sufficient evidence establishing that Vigne claim 1 would not have been obvious in view of Wang claim 39 and the teachings of the prior art, e.g., Cutt (Ex

[12] Cutt et al. (Cutt), "Analysis of Adenovirus Early Region 4-Encoded Polypeptides Synthesized in Productively Infected Cells," Journal of Virology, Vol. 61, No. 2, pp. 543-552 (February 1987) (Ex 2021).

2021). Therefore, Gencell preliminary motion 5 is denied.

**C. Simply pointing to differences between the cells carrying heterologous DNA integrated into the genome vis-a-vis episomally transfected cells is insufficient to establish nonobviousness between Vigne's "species" and Wang's "genus".**

Gencell further argues that transiently transfected cells are patentably distinct from cells having heterologous genes integrated into their genome. Gencell takes the position that expression levels from introduced genes depend on multiple factors including DNA copy number per cell, transcriptional efficiency, mRNA processing and stability, and protein processing and stability (citing Ex 1015). [Paper 44, p. 8.] According to Gencell, since the site of integration in the cell genome is random in transiently transfected cell lines, the level of transgene expression is unpredictable. Further according to Gencell, if the gene of interest has a toxic effect on cells, as is the case with a number of adenovirus proteins, the cell's ability to grow may be compromised. Thus, Gencell argues that identifying and isolating successful integrations of genes encoding adenoviral gene products can be problematic because cells may not grow any better than non-transformed under selectable pressure. [id.]

On the other hand, Gencell urges that cells having heterologous DNA integrated into the genome are patentably distinct from cells having the heterologous DNA carried on extrachromosomal episomes (id., pp. 7-8). In support of this position, Gencell cites Ex 1015, pp. 495-496, and suggests that transfection efficiency varies tremendously and often less than one in ten treated cells retain heterologous DNA carried on extrachromosomal episomes (Paper 44, pp. 7-8).

First, Wang's claims are generic with respect to whether heterologous DNA is

chromosomally integrated into the complementing cell line or is present episomally. Second, for reasons discussed above with respect to Gencell preliminary motion 2, Gencell has not satisfied its burden with respect to Gencell preliminary motion 5 either procedurally or substantively. We, therefore, find it unnecessary and we do not reach Wang's opposition to Gencell preliminary motion 5 or Gencell's Reply thereto.

Based on the foregoing, Gencell preliminary motion 5 is **denied**.

## VII. GENCELL PRELIMINARY MOTION 6

Gencell moves pursuant to 37 CFR § 1. 633(b) for judgment of no interference-in-fact between the claims of Wang and Perricaudet corresponding to Count 4, i.e., Wang claims 39-44 and 57 and Perricaudet claims 19-23, 25, 27 and 33. (Paper 45). Wang opposes (Paper 68); Gencell replies (Paper 87).

As noted above, Count 4 is alternatively defined by Vigne claim 1 or Wang claim 39 or Perricaudet claim 22 (FF 21).

According to Gencell, Perricaudet claim 22 is directed to a cell line comprising E1 and E4 genes integrated into its genome, wherein the E4 gene is under the control of an inducible promoter, whereas Wang claim 39 is directed to a cell line comprising E1 and E4 gene regions, wherein the E4 gene region is operably linked to an inducible promoter (Paper 45, p. 4). Gencell contends the cell lines of Perricaudet claim 22 and Wang claim 39 are two patentably distinct inventions because "[t]he cell lines of Wang '680 do not require that the E1 and E4 genes be integrated into the genome" (id.).

As an initial matter, in view of the amendment to Perricaudet claim 1, upon which Perricaudet claim 19 depends, Perricaudet claim 19 is now directed to a cell line

comprising, integrated into its genome, adenoviral genes necessary to support replication of a replication defective adenoviral vector, wherein E1 and E2 genes, but not E4 genes, have been rendered non-functional by deletion. Consequently, Perricaudet claims 21, 22 and 33, which recite cell lines comprising an E4 gene or ORFs 6 and 6/7 under control of an inducible promoter, no longer properly limit Perricaudet claim 1 from which they ultimately depend (see also Hearing Transcript, Paper 115, page 25, lines 1-6, in reference to Perricaudet claim 22).[13]

Gencell again argues that transiently transfected cells are patentably distinct from cells having adenoviral genes integrated into their genome (Paper 45, pp. 5-6).Gencell again refers us to Exs 1013 and 1015 per se (id.). This argument is unpersuasive for reasons given above (see § VI.C). Simply pointing to the differences between cells carrying heterologous DNA integrated into their genome vis-a-vis episomally transfected cells is insufficient to establish nonobviousness, especially where the differences result in expected results, e.g., integration into the genome results in stable, as opposed to transient, transfection. Reliance on vague citations to evidence, e.g., Exs 1013 and 1015 per se, in support of arguments is a procedural defect.

However, the amendments to Perricaudet to claims 1, 2 and 11 moot Gencell preliminary motion 6 as to Perricaudet claims 19, 20, 23, 25 and 27. Thus, for the

[13] Perricaudet claim 22, which recites a cell line comprising E1 and E4 genes integrated into its genome, depends upon claim 19, which recites a cell line comprising the genes necessary to complement the adenovirus of Perricaudet claim 1. However, Perricaudet claim 1 has been amended to recite an adenovirus wherein E1 and E2 genes, but not E4 genes, have been rendered non-functional by deletion (Paper 102).

reasons given above, Gencell preliminary motion 6 is denied as to Perricaudet claims 21, 22 and 33, which improperly depend on amended Perricaudet claim 1.

Based on the foregoing, Gencell preliminary motion 6 is **dismissed** as moot as to Perricaudet claims 19, 20, 23, 25 and 27 and otherwise **denied** as to Perricaudet claims 21, 22 and 33.

## VIII. WANG PRELIMINARY MOTION 1

Wang moves pursuant to 37 CFR § 1.633(b) for judgment that there is no interference-in-fact between any of Wang's involved claims, i.e., Wang claims 37-44, 46-48, 52, 54 and 56-57, and any of Perricaudet's involved claims, i.e., Perricaudet claims 1-3, 9, 12-28, 30, 33-35 and 40-42 (Paper 35). Gencell opposes with respect to Counts 1, 3 and 5 (Paper 59); Wang replies thereto (Paper 81).

38. Wang "offers no comment with respect to the potential interference between Vigne and Perricaudet, on the one hand, and Vigne and Wang on the other" (Paper 35, p. 16).

39. Gencell "agrees that no interference-in-fact exist[s] between the cell lines of Wang and those of Perricaudet based on the requirement for integration of the adenoviral genes into the genome" (Paper 59, p. 12).

### A. Count 1 and corresponding Wang and Perricaudet claims

Count 1 is directed to recombinant adenoviral vectors unable to replicate due to deficiencies in essential gene functions of the E2 region (FF 10). Wang claims 46 and 56 and Perricaudet claims 1-3, 9, 12-18, 28, 30, 35 and 40-41 correspond to Count 1 (FF 30). (No Vigne claims correspond to Count 1 (FF 30)).

40. The vectors of Wang claims 46 and 56 contain "at least a lethal deletion or mutation in two gene regions selected from the group consisting of the E1, E2A and E4 early gene regions" and requires "at most complementation of genes of the E1, E2A and E4 adenoviral early gene regions.

41. The vectors of Perricaudet claims 1-3, 9, 12-18, 28, 30 and 40-41, as currently amended, contain E1 and E2, but not E4, genes which have been rendered non-functional by deletion. The vector of Perricaudet claim 35 comprises ITR sequences, an encapsidation sequence, a heterologous DNA sequence, and an E4 region, which E4 region is the sole adenoviral region present.

Wang argues its claimed vectors "may not include deletions of E2B or the late gene regions, or promoters therefore (MLP-1) because the Wang claims specifically limit the maximum amount of complementation" (Paper 35, p. 18). In other words, the Wang claims do not permit deletion of the E2B region, whereas the Perricaudet claims require deletion of the E2B region (id., p. 19). Wang further argues that its claimed vectors "require lethal deletions or mutations in a gene" (id., p. 20, original emphasis), whereas the Perricaudet claims require the identified gene regions to "rendered non-functional 'by deletion'" (id., ¶ bridging pp. 20-21). "Stated otherwise, Wang's claims, calling for selective deletion of a gene function by deletion of that gene or a selective deletion within a region, do not suggest to those skilled in the art the desirability of deletion of an entire region, and most importantly, do not predict the success of that deletion, called for by the Perricaudet claims" (id., p. 21).

### 1. Perricaudet claims 1-3, 9, 12-18, 28, 30, 35 and 40-41 require deletion of the entire E2 region

In its opposition (Paper 59, p. 8), "Gencell responds that, with the exception of claim 35, the claims of Count 1 simply do not require deletion of a complete *region* as argued by Wang's Preliminary Motion 1."

42. However, Perricaudet claim 1 was amended subsequent to the declaration of this interference to recite a vector "wherein E1 genes have been rendered non-functional by deletion, and wherein E2 *genes*, but not E4 genes, have been rendered non-functional by deletion" (Paper 102, attachment pp. 1-2, emphasis added).

As pointed out by Wang in its reply (Paper 81, p. 2), "deletion of 'E2 genes', a plural term, ... is not satisfied by deletion of E2A."

### 2. deletion of E2 is patentably distinct from deletion of E2A

43. It is agreed that adenoviral region E2 including two regions, i.e., E2A and E2B, which encode proteins required for viral DNA replication.[14]

44. Dr. Curiel testified that E2A encodes a DNA binding protein, while E2B encodes polymerase and preterminal proteins, and that each of these three proteins is functionally distinct from the others and successful deletion and complementation of one is not predictive of deleting or complementing the others (Ex 2004, ¶¶ 7 and 10).

45. Dr. Curiel further testified that deletion of all of E2 (i.e., both E2A and E2B), as required by Perricaudet's claims, versus E2A alone, as required by Wang's claims, is not an intuitive variation because of the distinct functions provided for by the E2A and E2B proteins and because deletion of E2B would also delete sequences opposite

[14] See Paper 59, p. 3 where Gencell admits Wang fact 8 as set forth in Paper 35, p. 3.

thereto, e.g., the major late promoter that directs expression of late genes L1-L5 (id.).

We find Dr. Curiel's testimony to be highly credible and undisputed by Gencell in this regard.

**3. "deletion" as defined in Perricaudet '225 encompasses deletion in a region**

46. "Deletion" is defined in Perricaudet '225 (Ex 2002, p. 9, ¶ 4, emphasis added) to encompass "any suppression of the gene considered. . . .especially all or part of the coding region of the said gene, and/or all or part of the promoter region for transcription of said gene."

Therefore, Wang's argument of "selective deletion in a region" is a difference without a distinction in view of the express definition of "deletion" given in Perricaudet '225.

**4. conclusion as to Count 1 and its corresponding claims**

Based on the foregoing, we find no interference-in-fact between Wang claims 46 and 56 and Perricaudet claims 1-3, 9, 12-18, 28, 30, 35 and 40-41 corresponding to Count 1 because adenoviral vector claims requiring a deletion of both E2A and E2B, as recited by Perricaudet, do not anticipate or render obvious vector claims requiring a deletion of E2A and prohibiting a deletion of E2B.

**B. Count 2 and corresponding Wang and Perricaudet claims**

Count 2 is directed to complementing cell lines for adenoviral vectors unable to replicate due to deficiencies in essential gene functions of the E2 region (FF 10). Wang claim 48 and Perricaudet claims 19-20, 23 and 25-27 correspond to Count 2 (FF 31). (No Vigne claims correspond to Count 2 (FF 31)).

47. The complementing cell line of Wang claim 48 "supplies the function of the E2A and E4 early regions."

**1. Perricaudet claims 19-20, 23 and 25-27 comprise adenoviral E1 and E2, but not E4, genes**

48. Perricaudet claims 19-20, 23 and 25-27 all ultimately depend from now amended Perricaudet claim 1. Consequently, the complementing cell lines of Perricaudet claims 19-20, 23 and 25-27 comprise adenoviral E1 and E2, but not E4, genes.

**2. conclusion as to Count 2 and its corresponding claims**

Therefore, consistent with the discussion immediately above as well as with the grant of Gencell preliminary motion 2 above, we find no interference-in-fact between Wang claim 48 and Perricaudet claims 19-20, 23 and 25-27.

**C. Count 3 and corresponding Wang and Perricaudet claims**

Count 3 is directed to recombinant adenoviral vectors unable to replicate due to deficiencies in essential gene functions of the E4 region (FF 10). Wang claims 37-38, 46-47, 52, 54 and 56 and Perricaudet claims 1-3, 9, 12-18, 28, 30, 34 and 40-41 correspond to Count 3 (FF 32). (Vigne claim 33 also corresponds to Count 3 (FF 32)).

**1. Wang's corresponding claims require lethal deletion(s) and/or mutation(s) in the E4 region**

49. The vectors of Wang claims 37, 46, 54 and 56/46 comprise "at least two lethal deletions, two lethal mutations, or one lethal deletion and one lethal mutation in the E1 and E4 early gene regions" and, optionally, in the E2A region.

50. The vectors of Wang claims 38, 47, 54 and 56/47 comprise "at least two lethal deletions, two lethal mutations, or one lethal deletion and one lethal mutation in the E1

and E4 early gene regions" and prohibits any other lethal deletions and/or mutations (i.e., "requires for replication at most complementation of genes of both the E1 and E4 adenoviral early gene regions).

**2. Perricaudet claims 1-3, 9, 12-18, 28, 30 and 40-41 require a functional E4 region**

51. The vectors of Perricaudet claims 1-3, 9, 12-18, 28, 30 and 40-41, as currently amended, comprise "E1 genes . . . rendered non-functional by deletion, and . . . E2 genes, but not E4 genes, . . . rendered non-functional by deletion" (Paper 102).

**3. Perricaudet claim 34 requires E2 to be the sole early gene region**

52. The vector of Perricaudet claim 34 comprises "ITR sequences, an encapsidation sequence, a heterologous DNA sequence, and an E2 region, wherein the E2 region is the sole adenoviral early region." Thus, Perricaudet claim 34 encompasses a vector lacking its E1, E3 and E4 regions and, therefore, requiring complementation of at least the E1 and E4 gene regions (the E3 region is not required for viral replication).

Thus, contrary to Wang's assertion (Paper 35, p. 6, FF 19.), the E2 gene is not the sole adenoviral region of the claimed vector. Rather, E2 is the sole early region of the vector recited in Perricaudet claim 34, which is both silent as to any and all late genes and written in open-ended "comprising" language.

**4. conclusion as to Count 3 and corresponding Wang and Perricaudet claims**

Based on the foregoing, we find no interference-in-fact between Wang claims 37-38, 46-47, 52, 54 and 56 and Perricaudet claims 1-3, 9, 12-18, 28, 30 and 40-41, as

currently amended. However, an interference-in-fact exists between Wang claims 37-38, 46-47, 52, 54 and 56 and Perricaudet claim 34. Perricaudet claim 34 is directed to a species within Wang claim 37 and which is obvious over Wang claim 38 because the E3 region deleted in Perricaudet claim 34 is not required for viral replication, e.g., requiring complementation of at most E1 and E4 early gene regions. Similarly, it would have been obvious to retain the E3 region deleted in the species of Perricaudet claim 34 to arrive at the genus recited in Wang claim 38 since the E3 region is not required for viral growth and, therefore, needs no complementation for its deletion.

**D. Count 4 and corresponding Wang and Perricaudet claims**

Count 4 is directed to complementing cell lines for adenoviral vectors unable to replicate due to deficiencies in essential gene functions of the E4 region (FF 10). Wang claims 39-44 and 57 and Perricaudet claims 19-23, 25, 27 and 33 correspond to Count 4 (FF 33). (Vigne claims 1-6, 11-16, 20-21 and 23-25 also correspond to Count 4 (FF 33)).

53. The complementing cell lines of Wang claims 39 and 57/39 are "derived from a 293 cell" and supply "the function of the E1 early gene regions and the E4 early gene regions wherein nucleotide sequences encoding the E4 early gene region are operably linked to an inducible promoter." The cell line of claim 57/39 "supports the growth of an adenovirus which further comprises a deletion of the E3 gene region."[15]

54. Independent Wang claim 40 and claims dependent thereon, i.e., claims 41-44,

[15] It is unclear how Wang claim 57 further limits the cell line of claim 39 insofar as the E3 gene region is not required for adenoviral replication and, therefore, a cell line that additionally supports an E3 deletion does not provide any further complementary gene function.

are directed to DNA plasmids "comprising an inducible promoter operably linked to nucleotide sequences encoding a cytotoxic gene product of an adenoviral E4 gene or E4 early gene region." Dependent claims 41-44 limit claim 40 to specific inducible promoters.

55. According to Dr. Curiel, although DNA plasmids may contain genetic material, they are not cells and do not include ITRs or packaging sequences and are not encapsulated into infectious particles (Ex 2004, ¶ 42).

56. As noted above in regard to Gencell preliminary motion 6, the complementing cell line of Perricaudet claim 19, which depends upon Perricaudet claim 1 as now amended, is directed to a cell line comprising, integrated into its genome, adenoviral genes necessary to support replication of a replication defective adenoviral vector, wherein E1 and E2 genes, but not E4 genes, have been rendered non-functional by deletion. The cell line is further defined as having the E2 gene under the control of an inducible promoter (claim 20), e.g., an LTR promoter of MMTV (claim 25), as having a glucocorticoid receptor gene (claim 23), and as being derived from a parental 293 cell line (claim 27).

57. Further according to Dr. Curiel,

(a) the cell line of Wang claim 39 place multiple (i.e., E1 and E4) genes under the control of a single promoter, the cell line of Perricaudet claim 19 requires that only one of the genes being complemented for be under control of a single promoter (Ex 2004, ¶ 43), and

(b) E2 complementation is outside the scope of the cell line of Wang claim 39,

while nothing in the Perricaudet claims 19-23, 25, 27 or 33 preclude Perricaudet's cell lines from complementing for E2B (id., ¶ 44).

58. Perricaudet claims 19-20, 23 and 25-27 all ultimately depend from now amended Perricaudet claim 1.

59. Consequently, the complementing cell lines of Perricaudet claims 19-20, 23 and 25-27 comprise adenoviral E1 and E2, but not E4, genes.

60. Perricaudet claims 21, 22 and 33, however, expressly recite cell lines comprising an E4 gene or ORFs 6 and 6/7 under control of an inducible promoter.[16]

Wang reiterates its arguments (1) that the Wang cell line claims, i.e., claims 39 and 57/39, do not complement for E2B or late gene regions; (2) that the Wang claims call for one promoter for two genes, i.e., E1 and E4, whereas each adenoviral gene in the Perricaudet cell line must be under control of a separate promoter; and, (3) that Perricaudet's claimed cell lines are stably transfected (i.e., heterologous DNA is integrated into the cell's genome), while Wang's claimed cell lines are not so limited (i.e., encompass both transient and stable transfection) (Paper 35, pp. 22-23).

### 1. Perricaudet claims 19, 20 23, 25 and 27 no longer interfere with Wang claims 39-44 and 57, in view of Gencell's amendment to Perricaudet claim 1

Count 4 is directed to complementing cell lines for adenoviral vectors unable to replicate due to deficiencies in essential gene functions of the E4 region (FF 10). Therefore, insofar as the cell lines of Perricaudet claims 19, 20, 23, 25 and 27

[16] Perricaudet claims 21, 22 and 33, dependent on claim 19 which is in turn dependent on claim 1, recite cell lines comprising an E4 gene or ORFs 6 and 6/7 under control of an inducible promoter and, therefore, no longer properly limit Perricaudet claim 1 from which they ultimately depend.

complement replication defective adenoviral vectors wherein E4 functions are expressly functional, they no longer anticipate or render obvious cell lines which complement for lethal deletion and/or mutation of E4 gene function, i.e., the cell lines of Wang claims 39 and 57/39. Similarly, the cell lines of Perricaudet claims 19, 20, 23, 25 and 27 no longer render obvious a plasmid comprising an inducible promoter operably linked to nucleotide sequences encoding an E4 gene product as recited in Wang claims 40-44.

**2. Perricaudet claims 21, 22 and 33 no longer interfere with Wang claims 39-44 and 57, in view of Gencell's amendment to Perricaudet claim 1**

As noted above, while Perricaudet claims 21, 22 and 33 expressly recite cell lines comprising an E4 gene or ORFs 6 and 6/7 under control of an inducible promoter (FF 94), these cell lines must ultimately support replication of the ΔE2 adenoviral vector of amended Perricaudet claim 1, i.e., they must supply the function of both the E2A and E2B genes (FF 76). However, the cell lines of Wang claims 39 and 57/39 are silent as to whether they supply the function of the E2B gene insofar as they are required to at least complement genes of both the E1 and E4 early gene regions. Similarly, the open-ended "comprising" language of the plasmids of Wang claims 40-44 neither include nor exclude the presence of one or both E2 genes, E2A and/or E2B. Thus, while the complementing cell lines of Perricaudet claims 21, 22 and 33 may be a species within the genus recited by Wang claims 39 and 57, Wang has presented evidence via the testimony of Dr. Curiel that complementation of E2, i.e., E2A and E2B, is outside the scope of the cell line of Wang claim 39 (Ex 2004, ¶ 43). Similarly, the plasmids of Wang claims 40-44, which may be used to introduce adenoviral DNA, i.e., E4 gene

sequences, into a complementing cell line and which neither include nor exclude the presence of nucleotide sequences encoding E2 gene products, do not clearly anticipate or rendered obvious the cell lines of Perricaudet claims 21, 22 and 33.

Gencell's amendment of Perricaudet claim 1 has mooted its rebuttal argument that the Perricaudet cell line of claims 21, 22 or 33 need not complement for the E2B or late gene regions (Paper 59, p. 11).

**3. arguments based on number of promoters or stable transfection are unpersuasive**

Wang argues the Wang claims call for one promoter for two genes, i.e., E1 and E4, whereas each adenoviral gene in the Perricaudet cell line must be under control of a separate promoter inherently requires a narrow interpretation of Perricaudet claim 19 (Paper 35, pp. 22-23). As noted by Gencell in its reply (Paper 59, ¶ bridging pp. 11-12, original emphasis), "Claim 19 of Perricaudet does not state that *only* one complementing gene is under the control of an inducible promoter, but rather, that 'one of the complementing genes is under the control of an inducible promoter.'" Furthermore, Wang does not dispute Gencell's interpretation of Perricaudet claim 19 in its reply (Paper 81).

Wang also argues that Perricaudet's claimed cell lines are stably transfected (i.e., heterologous DNA is integrated into the cell's genome), while its claimed cell lines are not so limited (i.e., encompass both transient and stable transfection) (Paper 35, p. 23). However, Wang does not provide a specific citation to evidence supporting its argument that a stably transfected cell line is an unobvious species within the genus of transfected cell lines. (Similar arguments raised by Gencell in its preliminary motions 2,

5 and 6 were found lacking for reasons discussed above.)

**4. conclusion as to Count 4 and corresponding Wang claims 39-44 and 57 and Perricaudet claims 19-23, 25, 27 and 33**

Based on the foregoing, we find no interference-in-fact between Wang claims 39-44 and 57 and Perricaudet claims 19-23, 25, 27 and 33 which correspond to Count 4 because Perricaudet's claimed cell lines complement replication defective adenoviral vectors wherein E4 functions are expressly functional and thus Perricaudet's cell lines no longer anticipate or render obvious cell lines which complement for lethal deletion and/or mutation of E4 gene function, i.e., the cell lines of Wang claims 39 and 57/39, or render obvious a plasmid comprising an inducible promoter operably linked to nucleotide sequences encoding an E4 gene product as recited in Wang claims 40-44.

Moreover, insofar as Wang has presented evidence that complementation of E2, i.e., E2A and E2B, is outside the scope of the cell line of Wang claim 39 (Ex 2004, ¶ 43) and the plasmids of Wang claims 40-44 are silent as to E2 gene sequences, i.e., neither include nor exclude the presence of nucleotide sequences encoding E2 gene products, Wang claims 39-44 and 57 do not anticipate or render obvious cell lines which are required to provide the function of E2 genes as claimed in Perricaudet's corresponding claims.

**E. Count 5 and corresponding Wang and Perricaudet claims**

Count 5 is directed to recombinant adenoviral vectors unable to replicate due to deficiencies in both E2 and E4 regions (FF 10). Wang claims 37, 46, 54 and 56 and Perricaudet claim 42 correspond to Count 5 (FF 34). (None of Vigne's claims correspond to Count 5.)

As noted above (FF 26), Perricaudet claim 42 reads:

> 42. A replication-defective adenovirus comprising an adenoviral genome that requires, for replication, complementation *in trans* of an essential gene function in each of at least two or more adenoviral early regions selected from the group consisting of the E1, E2A, and E4 regions of an adenoviral genome,
>
> wherein the adenovirus comprises one or more functional early or late gene regions of an adenoviral genome and requires complementation of an essential gene function in each of at least the E2A and E4 regions,
>
> wherein the adenovirus comprises a heterologous DNA sequence.

The vector of Perricaudet claim 42 encompasses adenoviruses with deletions in (i) E2A and E4 or (ii) E1, E2A and E4 regions.

As noted above (FF 19), Wang claim 37 reads:

> 37. A replication-defective recombinant adenovirus, wherein the genome of said adenovirus contains at least two lethal deletions, two lethal mutations, or one lethal deletion and one lethal mutation in the E1 and E4 early gene regions, so that the recombinanat adenovirus requires for replication at most replication of genes of the E1, E2A and E4 adenoviral early gene regions, wherein said recombinant adenovirus genome additionally contains a transgene.

By its literal claim language, Wang claim 37 encompasses a replication defective adenovirus that at least requires complementation of E1 and E4 deletions but at most requires complementation of E1, E2A and E4 deletions for replication.

61. Similarly, Wang claim 46 encompasses a replication defective adenoviral vector that requires at least complementation of E1 and E4 deletions, but at most requires complementation of E1, E2A and E4 deletions.

62. Wang claim 54 limits the E4 region which is deleted to E4 ORF 6.

63. Wang claim 56 additionally requires deletion of non-essential gene region E3 in the vector of claim 46 (or 47).

Wang argues "that the recitation, in Wang claim 46, or indeed, in any of the Wang vector claims, that there be a maximum deletion of E1, E2A and E4 is not suggested as desirable by Perricaudet Claim 42" (Paper 35, p. 24). In other words, Wang argues that since Perricaudet claim 42 suggests a minimum deletion of E1, E2A and E4 and Wang claim 46 suggests a maximum deletion of E1, E2A and E4, there is no interference-in-fact. This argument is unpersuasive.

**1. Wang claims 37, 46, 54 and 56 and Perricaudet claim 42 each claim adenoviral vectors unable to replicate due to lethal deletion in their E2A , E4 and, optionally, E1 gene regions**

Clearly, the scope of Wang claims 37 and 46 overlaps the scope of Perricaudet claim 42. These claims each encompass an adenoviral vector unable to replicate because of loss of essential gene function in either their E2A and E4 or their E1, E2A and E4 gene regions. Furthermore, these claims each encompass losing essential gene function as a result of lethal deletion. Moreover, as noted above (FF 46), insofar as Perricaudet '225 (Ex 2002, p. 9) defines "deletion" to encompass deletion in a region, e.g., "all or part of the coding region of the said gene," these claims also each encompass lethal deletion in a gene region. Therefore, Wang claims 37 and 46 anticipate Perricaudet claim 42 and vice-versa. Wang did not argue Wang claims 54 and 56 separate from Wang claims 37 and 46 (see e.g., Paper 35, ¶ bridging pp. 4-5).

**2. conclusion as to Count 5 and its corresponding claims**

Based on the foregoing, we find that Wang claims 37, 46, 54 and 56 define the same patentable invention as Perricaudet claim 42 and vice-versa. 37 CFR § 1.601(n).

## F. Count 6 and corresponding Wang and Perricaudet claims

Count 6 is directed to complementing cell lines for adenoviral vectors unable to replicate due to deficiencies in essential gene functions of both E2 and E4 regions (FF 10). Wang claims 48 and 57 and Perricaudet claim 24 correspond to Count 6 (FF 35). (None of the Vigne claims correspond to Count 6).

64. Perricaudet claim 24 expressly recites a complementing cell line comprising E2 and E4 adenoviral genes under the control of an inducible promoter.[17]

65. Wang claims 48 and 57, in contrast, recite a complementing cell line that supplies the function of the E2A and E4 early gene regions operably linked to an inducible promoter.

The cell line of Wang claims 48 and 57 does not supply the function of E2B, as opposed to the cell line of Perricaudet claim 24 which does complement for E2B function (i.e., complementing for E2, by definition, complements for both E2A and E2B).

Wang argues (1) that the Wang cell line claims do not complement for E2B or late gene regions; (2) that the Wang claims call for one promoter for two genes, i.e., E1 and E4, whereas each adenoviral gene in the Perricaudet cell line must be under control of a separate promoter; and, (3) that Perricaudet's claimed cell lines are stably transfected (i.e., heterologous DNA is integrated into the cell's genome), while Wang's claimed cell lines are not so limited (i.e., encompass both transient and stable transfection) (Paper 35, pp. 22-23).

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[17] Perricaudet claim 24, which recites a cell line comprising E2 and E4 genes under the control of an inducible promoter, depends on claim 19, which recites a cell line comprising the genes necessary to complement the adenovirus of Perricaudet claim 1. However, Perricaudet claim 1 has been amended to recite an adenovirus wherein E1 and E2 genes, but not E4 genes, have been rendered non-functional by deletion (Paper 102).

**2. conclusion as to Count 6 and corresponding Wang claims 48 and 57 and Perricaudet claim 24**

For the above reasons, we find no interference-in-fact between Wang claims 48 and 57 and Perricaudet claim 24 which correspond to Count 6 because Wang claims 48 and 57 exclude complementation of missing essential E2B gene function, whereas Perricaudet claim 24 expressly requires complementation of E2B gene function.

We are unpersuaded by unsupported attorney arguments asserting (a) that Wang claims call for one promoter for two genes, whereas each adenoviral gene in the Perricaudet cell line must be under control of a separate promoter or (b) that Perricaudet's stably transfected cell line is an unobvious species of a transfected cell line genus for reasons given above.

**G. Summary**

Based upon the foregoing, we grant Wang preliminary motion 1 as to Counts 1, 2, 4 and 6 and their corresponding Wang and Perricaudet claims; we further grant Wang preliminary motion 1 as to Count 3 only as to corresponding Perricaudet claims 1-3, 9, 12-18, 28, 30 and 41-42, but deny it as to Wang claims 37-38, 46-47, 52, 54 and 56 and Perricaudet claim 34; and, we deny Wang preliminary motion 1 as to Count 5 and corresponding Wang claims 37, 46, 54 and 56 and Perricaudet claim 42.

## IX. GENCELL PRELIMINARY MOTION 4

Gencell moves pursuant to 37 CFR § 1.633(c)(1) to substitute Gencell's "Proposed count 3" for existing Count 3; to designate Perricaudet claims 34, 43-55 and 61-62 as corresponding to Gencell's "Proposed count 3" and to designate Wang claims 37-38, 46-47, 52, 54 and 56 as corresponding to Gencell's "Proposed count 3" (Paper

43). Wang opposes (Paper 66); Gencell replies (Paper 78).

According to Gencell, none of the Vigne '175 claims should be designated as corresponding to Gencell's "Proposed count 3" (Paper 43, pages 2-3).

As a preliminary matter, we note that proposed new Perricaudet '225 claims 43-64 have not been entered (Papers 100 and 103).

Present count 3 is defined alternatively by

(a) Vigne claim 33, directed to a replication defective recombinant adenovirus having where **all or part of E1 and all of E4**, consisting of specified nucleotides, deleted;

(b) Wang claim 37, directed to an adenoviral vector having a lethal deletion or mutation in at least two gene regions selected from the **E1, E4 and, optionally, E2A** regions; or,

(c) Perricaudet claim 34, directed to a replication defective recombinant adenovirus wherein E2 is the only early region present, i.e., all of **E1, E3 and E4** have been deleted (FF 17).

66. Gencell's "Proposed count 3" reads (Paper 43, p. 2):

> A replication defective recombinant adenovirus comprising:
> ITR sequences;
> an encapsidation sequence, and
> a heterologous DNA sequence,
> wherein E1 genes have been rendered non-functional by deletion, and wherein E4 genes, but not E2 genes, have been rendered non-functional by deletion.

67. Gencell's "Proposed count 3" is *de facto* defined by **unentered** proposed Perricaudet claim 43, wherein E1 and E4, but not E2 genes have been deleted.

68. We note that Perricaudet '225 defines "deletion" as follows (Ex 2002, p. 9):

> [b]y deletion, there is understood for the purposes of the invention, any suppression of the gene considered. This may be especially by all or part of the coding region of the said gene, and/or all or part of the promoter region for transcription of the said gene. The suppression can be carried out by digestion by means of appropriate restriction enzymes, and then ligation, according to conventional molecular biology techniques, as illustrated in the examples.

69. Thus, Gencell's "Proposed count 3" differs from the Perricaudet claim 34 alternative of present Count 3 in reciting "wherein E1 genes have been rendered non-functional by deletion, and wherein E4 genes, but not E2 genes have been rendered non-functional by deletion" versus "wherein the E2 region is the sole adenoviral early region," respectively. In other words, "Proposed count 3" allows for the presence of nonessential gene region E3.

According to Gencell, Count 3 is improper for three reasons:

1. Count 3 is allegedly in conflict with Wang claim 37 which requires at most complementation of E1, E2A and E4 genes for replication.

2. Count 3 allegedly circumscribes more than one separately patentable invention.

3. Count 3 is narrower in scope than original Perricaudet claim 1. [Paper 43, pages 7-8].

First, since E3 is a non-essential gene region, i.e., it is not required for viral replication, present Count 3 is not in conflict with Wang claim 37. Second, Gencell has failed to explain what other separately patentable inventions are circumscribed within Count 3. Third, assuming without deciding that this argument is correct, it is moot in

view of Gencell's amendment to Perricaudet '225 claims 1, 2, and 11.

Moreover, here, as in Gencell preliminary motion 1, Gencell has failed to "show the patentability to the applicant of all claims in or proposed to be added to, the party's application which correspond to each count." 37 CFR § 1.637(c)(1)(ii).

Rule 637(c)(2)(iii) requires movant to establish that the subject matter of the claim, i.e., each element of the claim, is described in the specification in the manner required by the first paragraph of 35 U.S.C. § 112. See also § 21 of the STANDING ORDER. According to 37 CFR § 1.637(c)(2)(iii), the movant must "show the patentability" to the applicant of each claim proposed to be amended or added. A note of the Chief Administrative Patent Judge addresses the issue of how one should interpret rules that require a party to "show the patentability" of a claim in 1217 Off. Gaz. Pat. & Tm. Office 17-18 (December 1, 1998). The notice explains:

> The requirement of the rules that a party "show the patentability" of a claim may have led to some confusion as to precisely what is required to comply with the rules. This notice provides guidance with respect to the requirement to "show the patentability."
>
> The requirement that a party "show the patentability" of a claim should not be construed as requiring a party to prove a negative, i.e., that there is no prior art which would anticipate the claim under 35 U.S.C. § 102 or render the claims unpatentable under 35 U.S.C. § 103. In this respect, the burden of establishing that a claim is not patentable generally falls on the party or individual alleging unpatentability. See e.g., 35 U.S.C. § 102 which provides that an applicant is "entitled to a patent unless * * *." See also Horton v. Stevens, 7 USPQ2d 1245, 1246-47 (Bd. Pat. App. & Int. 1988). Consistent with 37 CFR § 1.601, which provides that the rules should be construed to secure the just, speedy and inexpensive determination of interference, the rules requiring a party to "show the patentability" of a claim normally should be interpreted as requiring that a party establish that the subject matter of the claim is described in the specification in the manner required by the first paragraph of 35 U.S.C. § 112. See also 37 CFR § 1.75(d)(1). The requirement can most effectively

be met by reproducing the claim, and following each element recited in the claim, and within braces {} and in bold, insert a specific reference to the column and line number and/or drawing figure and numeral where the element is described in the specification.

An exception would be a situation where a party files a preliminary motion under 37 CFR § 1.633(i) in response to an opponent's preliminary motion under 37 CFR § 1.633(a) for judgment. Since the party knows the basis for the opponent's preliminary motion for judgment, the party should also "show the patentability" of the claims proposed to be added by the preliminary motion under 37 CFR § 1.633(i) vis-a-vis the opponent's basis in the preliminary motion under 37 CFR § 1.633(a). Compare 37 CFR §§ 1.111(c) and 1.119 [(1998)].

The precise basis upon which a party is required to "show the patentability" necessarily will vary on a case-by-case basis.

Here, as in Gencell preliminary motion 1, Gencell has failed to "show the patentability to the applicant of all claims in or proposed to be added to, the party's application which correspond to each count. See 37 CFR § 1.637(c)(1)(ii). Thus, in addition to being substantively defective, Gencell preliminary motion 4 is also procedurally defective. Thus, Gencell has not shown that it is entitled to the relief requested or that substitution of the count is required.

Therefore, based on the foregoing, Gencell preliminary motion 4 is **denied**.

## X. GENCELL PRELIMINARY MOTION 7

Gencell moves pursuant to 37 CFR § 1.633(c)(1) to substitute Gencell "Proposed count 5" for present Count 5 and to designate Wang claims 46, 54 and 56 and Perricaudet claim 42 as corresponding to "Proposed count 5" (Paper 46). Wang does not oppose.

Gencell preliminary motion 7, when considered in light of the evidence relied upon in support of the motion, establishes a sufficient basis for substituting Gencell's

"Proposed count 5" for present count 5.

Wang claims 37, 46, 54 and 56 correspond to present Count 5 (FF 34). According to Gencell, "Proposed Count 5 is directed to a replication defective adenovirus which has deletions in E1, E2A and E4" (Paper 46, p. 5).

70. Wang claim 37 reads:

> 37. A replication-defective recombinant adenovirus, wherein the genome of said adenovirus contains at least two lethal deletions, two lethal mutations, or one lethal deletion and one lethal mutation in the E1 and E4 early gene regions, so that the recombinant adenovirus requires for replication at most replication of genes of the E1, E2A and E4 adenoviral early gene regions, wherein said recombinant adenovirus genome additionally contains a transgene.

By its literal claim language, Wang claim 37 encompasses a replication defective adenovirus that at least requires complementation of E1 and E4 deletions but at most requires complementation of E1, E2A and E4 deletions for replication. Gencell has offered no explanation as to why Wang claim 37 should not correspond to Gencell's "Proposed count 5".

Therefore, Gencell preliminary motion 7 is **granted** subject to the APJ taking further appropriate action with respect to claim 37.

## XI. GENCELL PRELIMINARY MOTION 9

Contingent on the denial of Gencell preliminary motion 6, Gencell moves pursuant to 37 CFR § 1.633(c)(1) to substitute Gencell's "Proposed count 4" for present Count 4 and to designate Wang claims 39-44 and 57 and proposed new Perricaudet claims 56-60 as corresponding to "Proposed count 4" (Paper 48). Wang opposes (Paper 70); Gencell replies (Paper 80).

Gencell's "Proposed Count 4" is defined in the alternative by **unentered** new proposed Perricaudet claim 56 (Paper Nos. 100 and 103). Gencell has not designated any pending Vigne or Perricaudet claim as corresponding to its "Proposed count 4". As to unentered new proposed Perricaudet claims 56-60, Gencell has failed to satisfy the requirements of 37 CFR. 1.637(c)(1)(ii). Furthermore, according to Gencell, "Proposed Count 4 is of the same scope as Count 4 as declared" (Paper 48, page 5) and "is directed to a cell line for complimenting [sic] an adenovirus having deletions in the E1 and E4 regions" (id, page 6).[18] Gencell has failed to show that it is entitled to the relief required, i.e., why Gencell's "Proposed count 4" should be substituted for present Count 4 given that "Proposed count 4" is admittedly of the same scope as Count 4 as declared.

Based on the foregoing, Gencell preliminary motion 9 is **denied**.

## XII. GENCELL PRELIMINARY MOTION 10

Gencell moves pursuant to 37 CFR § 1.633(f) for benefit for the purpose of priority of the filing dates of Perricaudet PCT, Perricaudet FR '590 and Perricaudet FR '596 for the subject matter of Gencell's "Proposed Count 1." (Paper 49). Wang opposes (Paper 71); Gencell replies (Paper 88).

This motion is moot in view of the denial of Gencell's preliminary motion 1 to substitute Gencell's "Proposed count 1" for present Count 1.

Therefore, Gencell preliminary motion 10 is **dismissed** as moot.

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[18] According to Gencell proposed new Perricaudet claim 56 corresponds to the cell line of original claim 19, which depended on the subject matter carved out of claim 1 [by amendment]" (Paper 48, p. 4).

## XIII. GENCELL PRELIMINARY MOTIONS 12, 13 and 15

In Gencell Preliminary motions 12, 13 and 15 Gencell moves pursuant to 37 CFR § 1.633(f) for benefit for the purpose of priority of the filing dates of Perricaudet PCT, Perricaudet FR '590 and Perricaudet FR '596 for the respective subject matter of Gencell's "Proposed counts 3, 4 and 6" (Papers 51, 52 and 54). Wang opposes motions 12 and 15 (Papers 72 and 74); Gencell replies thereto (Papers 89 and 91).

These motions are moot in view of the denial of Gencell preliminary motions 4, 9 and 8, which denied substitution of Gencell's "Proposed counts 3, 4 and 6" for present Counts 3, 4 and 6.

Therefore, Gencell preliminary motions 12, 13 and 15 are **dismissed** as moot.

## XIV. GENCELL PRELIMINARY MOTION 14

Gencell moves pursuant to 37 CFR § 1.633(f) for benefit for the purpose of priority of the filing dates of Perricaudet PCT, Perricaudet FR '590 and Perricaudet FR '596 for the subject matter of Gencell's "Proposed count 5" (Paper 53). Wang opposes (Paper 73); Gencell replies (Paper 90).

Gencell preliminary motion 14 stands on a different footing than its preliminary motions 12, 13 and 15 because Gencell preliminary motion 7, Gencell's motion to substitute "Proposed count 5," has been granted.

Gencell's "Proposed count 5" is of narrower scope than original Count 5, insofar as it requires deletion/mutation in three, as opposed to only two early regions, i.e., in E1, E2A and E4. Gencell has failed to show that any of its earlier applications (Perricaudet PCT, Perricaudet FR '590 and Perricaudet FR '596) constitutes a

constructive reduction to practice of the subject matter of the new count as required by 37 CFR § 1.637(f)(3). Thus, Gencell has failed to meet its burden of proof by showing it is entitled to the relief requested. For at least this reason, Gencell's preliminary motion 14 is **denied**.

## XV. GENCELL PRELIMINARY MOTION 11

Gencell moves pursuant to 37 CFR § 1.633(f) for benefit for the purpose of priority of the filing dates of Perricaudet PCT, Perricaudet FR '590 and Perricaudet FR '596 for the subject matter of Gencell's "Proposed count 2" (Paper 50). Wang does not oppose.

This motion is moot in view of the dismissal of contingent Gencell preliminary motion 3 to substitute "Proposed count 2" for present Count 2.

Therefore, Gencell preliminary motion 11 is **dismissed** as moot.

## XVI. WANG PRELIMINARY MOTION 4

Wang moves pursuant to 37 CFR § 1.633(a) for judgment that Perricaudet claim 42 is unpatentable for failure to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph (Paper 38). Gencell opposes (Paper 62); Wang replies (Paper 84).

As noted above (FF 26), Perricaudet claim 42 reads:

> 42. A replication-defective adenovirus comprising an adenoviral genome that requires, for replication, complementation *in trans* of an essential gene function in each of at least two or more adenoviral early regions selected from the group consisting of the E1, E2A, and E4 regions of an adenoviral genome,
>
> wherein the adenovirus comprises one or more functional early or late gene regions of an adenoviral genome and requires complementation of an essential gene function in each of at least the E2A and E4 regions,

wherein the adenovirus comprises a heterologous DNA sequence.

The vector of Perricaudet claim 42 encompasses adenoviruses with deletions in (i) E2A and E4 or (ii) E1, E2A and E4 regions.

71. Perricaudet '225 was filed with thirty (30) original claims (Ex 2002, p. 35). Thus, Perricaudet claim 42 is not an original claim.

**A. Wang's position**

According to Wang, the Perricaudet '225 application does not describe "deletion of an E2A region, alone, or together with other regions, such as E1 and E4, as recited in Claim 42, as an aspect of its invention" (Paper 38, p. 4). Further according to Wang, Perricaudet '225 does teach deletion of the E2 region, but a skilled artisan would not recognize a teaching to delete all of E2 as a teaching to delete E2A (id., p. 5). Still further according to Wang, although claim 42 encompasses deletion of both E2A and E2B, deleting E2A implies that E2B is not deleted unless otherwise specified (id.). In short, Wang contends that Gencell was aware of the E2A region when it filed Perricaudet '225 but did not identify the E2A region as potential target for deletion and complementation (id.).

72. Dr. Curiel testified for Wang that

> The E2B and late proteins are functionally distinct from those encoded by E1, E2A, and E4 gene gene [sic] regions, and therefore, the successful deletion and complementation of one of these gene functions is not predictive with respect to deleting and complementing for any another [sic] gene function, singly or in combination. Even the difference between eliminating the function of E2 versus E2A alone is not merely an intuitive variation because of the distinct functions provided for by E2A and E2B encoded proteins. This is underscored because of the importance of sequences located opposite to the E2B region, namely the major late promoter that directs the expression of late genes (L1-L5)

> encoding capsid proteins required for virion formation. (See, e.g., Exhibit 2007, p. 41, fig. 1). the [sic] late major promoter (MLP), which is required for expression of the late genes, overlaps with respect to the E2B gene region but is on the opposite strand (Exhibit 2007, p. 41, fig. 1). On this basis, deletion of the E2B gene region would also be deleterious with respect to late gene expression and thus, virion production, even if the late genes were not deleted from the vector. These functions cannot be complemented for by a host cell, but instead, are dependent on a second "helper" virus (Exhibit 2008, abstract and p. 3858, col. 2, ¶ 1). That is, these functions cannot be complemented for by a host cell, but instead, require selecting a second virus to express the missing gene functions at the appropriate time and level. (Exhibit 2008, abstract and p. 3858, col. 2, ¶ 1). [Ex 2017, ¶ 14.]

**B. Legal standard**

Section 112, first paragraph, provides that the "specification shall contain a written description of the invention." To fulfill the written description requirement, the patent specification must describe an invention in sufficient detail that one skilled in the art can clearly conclude that the inventor invented what is claimed. Lockwood v. Am. Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). The disclosure as originally filed does not, however, have to provide in haec verba support for the claimed subject matter at issue. See Fujikawa v. Wattanasin, 93 F.3d 1559, 1570, 39 USPQ2d 1895, 1906 (Fed. Cir. 1996). In order to comply with the written description requirement, the specification "need not describe the claimed subject matter in exactly the same terms as used in the claims; it must simply indicate to persons skilled in the art that as of the [filing] date the applicant had invented what is now claimed." Eiselstein v. Frank, 52 F.3d 1035, 1038, 34 USPQ2d 1467, 1470 (Fed. Cir. 1995) (citing Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) and In re Wertheim, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA

1976)).

**C. Gencell's response**

In its opposition (Paper 62, ¶ bridging pp. 5-6, original emphasis),

> Gencell responds that Claim 1 of the Perricaudet '225 application, as filed, was directed to a defective adenovirus in which "the E1 gene and at least one of the E2, E4 and L1-L5 *genes* is nonfunctional." When viewed in connection with, *inter alia*, Example 1, which discloses mutants having the E2A region deleted and a substantial portion of E2B intact, one skilled in the art would clearly recognize that Perricaudet was and is clearly in possession of a vector as currently claimed in Claim 42.

According to Gencell, mutant mt1 of Perricaudet '225 Example 1 is a vector wherein all of the E2A region is deleted and a substantial portion of the E2B region is left intact (id., sentence bridging pp. 4-5).

73. Example 1 in Perricaudet '225 discloses various mutants, including mutant mt1 said to have been prepared by ligating adenoviral 5 (Ad5) nucleotides 0-20642(Saul) and (Saul) 33797-35935 (Ex 2002, p. 16, ll. 14-15). In other words, mutant mt1 comprises an adenoviral genome missing nucleotides 20643-33796.

Gencell argues that (Paper 62, p. 5),

> [o]ne skilled in the art at the time of filing of the Perricaudet '225 application would recognize the E2A region as residing between Nuc 22420-27090. EX 1008, EX 1011 (Adenoviral Maps). One skilled in the art would further recognize the E2B region as residing between Nuc 4050-27092. EX 1008, EX 1011 (Adenoviral Maps). Accordingly, one skilled in the art would readily recognize that mutant mt1 was a vector having the E2A region deleted but having a substantial portion of the E2B region (4050-20642) intact.

74. Exhibit 1008 is an excerpt from GENETIC MAPS: Locus Maps of Complex Genomes, Book 1 "Viruses," sixth edition, S. O'Brien, ed., Cold Spring Harbor Laboratory Press (1993), consisting of six unnumbered pages. One page is titled

"Contents" and another "Genetic Map of Adenovirus." A three page table is entitled "Genetic map of the adenovirus type 2 genome (Modified and updated from ref. 95)."

75. Exhibit 1011 is a ten page set of adenoviral region maps for both adenovirus types 5 and 2. No source(s) is cited as the basis for preparing the maps of Exhibit 1011.

76. Gencell does not point us to, and we do not find, any testimony by a skilled artisan as to what essential gene function would have to be complemented for in order for the mt1 mutant to replicate.

**D. Analysis**

As noted by Wang in its motion, Perricaudet '225 does not provide a literal description of an adenoviral vector within the scope of Perricaudet claim 42. However, a specification is not required to provide a literal description of the claimed invention so long as it describes the invention in sufficient detail that one skilled in the art can clearly conclude that the inventor invented what is claimed. Gencell points us to mutant mt1 and original claim 1 of Perricaudet '225 to show that it was in possession of the vector of Perricaudet '225 claim 42.

77. Perricaudet '225 original claim 1 reads:

> 1. A defective recombinant adenovirus comprising:
> -the ITR sequences,
> -a sequence permitting encapsulation,
> -a heterologous DNA sequence,
> and in which the E1 gene and at least one of the E2, E4 and L1-L5 genes is non-functional.

On its face, original claim 1 refers to a non-functional E2 gene. We find the testimony of Dr. Curiel that "the difference between eliminating the function of E2

versus E2A alone is not merely an intuitive variation because of the distinct functions provided for by E2A and E2B encoded proteins" (Ex 2017, ¶ 14) to be highly credible. In other words, while Perricaudet claim 42 requires deletion of E2A, Perricaudet original claim 1 calls for deletion of E2.

We note that Perricaudet original claim 7 recites

> 7. An adenovirus according to claim 1, characterized in that it comprises;
> -the ITR sequences
> -a sequence permitting the encapsulation,
> -a heterologous DNA sequence, and
> -a region carrying the gene or part of the gene E2.

However, we have no testimony what "the gene or part of the gene E2" would have meant to a skilled artisan. Furthermore, Gencell did not rely on original claim 7 in its opposition.

Thus, in view of the express language of Perricaudet original claim 1 and the testimony of Dr. Curiel that deletion of E2A is not an intuitive variation of deletion of E2, original claim 1 alone is insufficient to show that Perricaudet was in possession of the invention of Perricaudet claim 42.

In addition, Gencell has not explained why a skilled artisan would have read original claim 1 "in connection with" mutant mt1, i.e., why the skilled artisan would have deleted E2A as a variation of deleting all of E2. While it may have been possible to do so, we credit the testimony of Dr. Curiel that the distinct functions provided for by E2A and E2B encoded proteins would have suggested otherwise.

To the extent that mt1 is said to delete all of E2A and some of E2B from a type 5 (Ad5) adenovirus, while leaving much of E2B intact, we find Gencell's argument that

"the E2B genes encoding DNA polymerase and the preterminal protein, [are] intact", to be attorney argument. Gencell has not pointed us to evidence establishing that specific coding regions within the E2B gene of Ad5 were known in the art to encode DNA polymerase and preterminal protein at the time Perricaudet '225 was filed. Exhibit 1008 was published in 1993 and apparently depicts a genetic map of a type 2 (Ad2) adenovirus. Exhibit 1011 is undated. Gencell has not provided evidence, e.g., by expert testimony, to establish that the genetic maps of adenovirus types 2 and 5 were recognized as essentially identical as of Perricaudet's '225 filing date.

Finally, we note that adenovirus is a double-stranded virus and deletion of nucleotides 20643 through 33796 would be expected to occur in both strands. See the testimony of Dr. Curiel relating to the importance of sequences located opposite to the E2B region (Ex 2017, ¶ 14).

Based on the foregoing, Wang preliminary motion 4 is **granted**.

## XVII. WANG PRELIMINARY MOTION 3

Wang moves pursuant to 37 CFR § 1.633(a) for judgment that Perricaudet claims 1-3, 9, 12-28, 30, 33-35 and 40-42 are unpatentable under 35 USC § 112, first paragraph, as not enabled throughout their scope (Paper 37). Gencell opposes (Paper 61); Wang replies (Paper 83).

Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); In re Wands, 858 F.2d 731, 736-737, 8

USPQ2d 1400, 1404 (Fed. Cir. 1988); In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the first paragraph of section 112 requires that the scope of protection sought in a claim bears a reasonable correlation to the scope of enablement provided by the specification). Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

An analysis of whether the claims at issue are supported by an enabling disclosure requires a determination of whether the supporting disclosure contained sufficient information regarding the subject matter of the claims at issue as to enable one skilled in the pertinent art to make and use the claimed invention. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. (footnote omitted). Wands, 858 F.2d at 737, 8 USPQ2d at 1404.

In considering an enablement rejection, the following passage from PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996) is instructive.

> In unpredictable art areas, this court has refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one or a few embodiments and do not demonstrate with reasonable specificity how to make and use other

> potential embodiments across the full scope of the claim. See, e.g., In re Goodman, 11 F.3d 1046, 1050-52, 29 USPQ2d 2010, 2013-15 (Fed. Cir. 1993); Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d. 1200, 1212-14, 18 USPQ2d 1016, 1026-28 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991); In re Vaeck, 947 F.2d at 496, 20 USPQ2d at 1445. Enablement is lacking in those cases, the court has explained, because the undescribed embodiments cannot be made, based on the disclosure in the specification, without undue experimentation. But the question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." Atlas Powder Co. v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

The Patent and Trademark Office Board of Appeals summarized the point well when it stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Ex parte Jackson, 217 USPQ 804, 807 (1982).

In view of our decision above granting Gencell preliminary motion 2 and granting-in-part Wang preliminary motion 1 for judgments of no interference-in-fact, this motion is moot as to Perricaudet claims 1-3, 9, 12-18, 30, 33, 35 and 40-41. Therefore, we limit our review of enablement to Perricaudet's adenoviral vector claims 34 and 42.

As noted above (FF 20), adenovirus Perricaudet claim 34 reads:

> 34. A replication defective recombinant adenovirus comprising
> ITR sequences,
> an encapsulation sequence,
> a heterologous DNA sequence, and an E2 region,
> wherein the E2 region is the sole adenoviral early region.

As noted above (FF 26), adenovirus Perricaudet claim 42 reads:

> 42. A replication-defective adenovirus comprising an adenoviral genome that requires, for replication, complementation *in trans* of an essential gene function in each of at least two or more adenoviral early regions selected from the group consisting of the E1, E2A, and E4 regions of an adenoviral genome,
>
> wherein the adenovirus comprises one or more functional early or late gene regions of an adenoviral genome and requires complementation of an essential gene function in each of at least the E2A and E4 regions,
>
> wherein the adenovirus comprises a heterologous DNA sequence.

Wang argues that the vast claim scope presents three obstacles to full enablement. First, the claims encompass adenoviruses with deletion of late gene functions which requires the use of helper viruses for complementation, thereby presenting toxicity issues in a complementing cell. According to Wang, preparation of replication-defective recombinant adenoviruses with deletions of ΔE2B, and deletions of late genes ( ΔL1-L5) are nowhere enabled in the Perricaudet '225 application (Ex 2002). Second, deletion of more than about 11Kb of the genome renders the adenovirus unstable, leading to unpredictable recombinations that render the adenovirus useless. Finally, the Perricaudet '225 application fails to enable a skilled artisan to provide complementation for every adenoviral species embraced, e.g., canine, bovine, murine, porcine and avian, when the replication defective adenovirus is other than a human adenovirus. Specifically, Wang argues that very few adenoviral genomes have been demonstrated to be subject to rescue and that Perricaudet '225 (Ex 2002) only discusses human type C adenovirus, without providing instructions, directions, sources or the like to one of ordinary skill in the art that would permit the identification of other adenovirus species and/or types. [Paper 37, pp. 12, 15 and 18.]

Below is an analysis of relevant enablement factors and associated evidence, including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the quantity of experimentation necessary, with respect to the claims subject to the enablement rejection.

**A. Breadth of claims**

Perricaudet claims 34 and 42 broadly encompass adenoviral vectors deleted of essential adenoviral genes of any species or type of adenovirus.

**B./C. Nature of the invention and Level of skill in the art**

The nature of the invention, i.e., adenoviral vectors, is complex and requires a high level of skill as evidenced by the prior art of record. A relatively high level of skill in the art is consistent with the testimony of Dr. Curiel, who testified for Wang, that a person of ordinary skill in the art would be knowledgeable in adenovirus biology, adenoviral vectors and adenoviral vector complementation systems and have an M.D. or Ph.D. with at least two years of post-graduate experience (Ex 2017, ¶ 6).

**D. State of the prior art**

**1. knowledge of the Ad2 and Ad5 adenoviral genome at the time of the invention was extensive**

By 1992, knowledge of the adenovirus genome was extensive, including the viral life cycle, DNA replication, transcription and RNA processing, and regulation of virus gene expression.

78. According to Perricaudet '225, "[t]here are various adenovirus serotypes whose

structure and properties vary somewhat. Nevertheless, these viruses exhibit a comparable genetic organization, and the information described in the present application can be easily reproduced by persons skilled in the art for any type of adenovirus" (Ex 2002, p. 5, ll. 5-10).

**2. "singly-deficient" adenoviral vectors were known**

79. The first generation of replication-defective adenoviral vectors deleted the E1 region (and optionally the nonessential E3 region) from the adenoviral genome and replaced it with a foreign gene of interest or ("transgene"). Without E1A there is no transcription of the rest of the early genes, thereby preventing viral replication. Such vectors are capable of infecting a cell only once and no viral propagation occurs. [Ex 1010, pp. 616-620]

80. Dr. Curiel testified that no complementing cell line has ever been described that could complement late genes or vectors deleted of the entire E2 region (Ex 2017, ¶ 20).

**3. adenoviral vectors lacking required gene function must be grown by complementation**

Since replication-defective adenoviral vectors lack required gene functions, the products of the missing gene(s) must be supplied by a source other than the viral genome. Complementation by one of two methods is possible - use of complementing cell lines or use of helper viruses.

**a. use of a helper virus**

Replication-defective adenoviral vectors can be grown using a helper virus, e.g., a wild-type adenovirus or an Ad2-simian virus 40 hybrid (Ex 1010, p. 621, ¶ bridging cc.

2-3).

81. Dr. Curiel testified that the only way to complement for all early and late gene regions, defective ITRs and packaging sequences would be to use a helper virus (Ex 2017, ¶ 14).

82. Dr. Curiel further testified that:

> [d]erivation of a helper virus capable of complementing a particular set of adenoviral late gene deletions successfully (i.e., at non-toxic levels) for any given complementing cell line is not trivial or predictable. Employing a helper virus will invoke infection related toxicities that are independent of viral gene expression. For example, the capsid proteins of the helper virus, especially the fiber (Exhibit 2002, p. 26, l. 19-20), are directly toxic to cells. [Ex 2017, ¶15, p. 7.]

83. According to Dr. Curiel,

> [e]ven with the use of a helper virus, extensively deleted vectors are difficult to produce, even today. One critical requirement is inherent to the adenoviral genome itself. The recombinant genome must be at least 75% of the wildtype genome (approximately 25 kb). Smaller genomes are unstable and undergo rearrangments. The extensive deletions embraced by Perricaudet's vectors claims would not satisfy this minimum and the '225 application fails to teach this essential requirement. For example, the '225 application describes that a vector deleted of all but the E2 gene region is 12 kb (Ex 2002, Example 3, p. 20, l. 9). One of skill in the art would recognize that an adenoviral genome cannot be packaged into infections virions if the size is too small. [Ex 2017, ¶16, p. 7.]

84. Further according to Dr. Curiel,

> [t]here are many technical differences between construction of adenoviruses with some or all late gene regions deleted. In this regard, trans-complemented gene functions must be sufficient for virion production but cannot be expressed at toxic levels that kill the supporting cell lines. Thus one skill[ed] in the art would not consider devising non-toxic trans-complementation via a helper virus to suggest the complementation restricted vectors of Wang's claims and vastly different technical considerations. (Exhibit 2008, abstract and p. 3858, col. 2 ¶1). [Ex 2004, p. 8.]

**b. use of complementary cell lines for singly-deficient adenoviral vectors was known**

85. Dr. Curiel testified that

> [t]he first cell line shown to complement for deficient E4 regions was derived from Vero cells (Exhibit 2014, Abstract), however, this same cell line was not able to complement for other adenoviral gene region deficiencies... (Ex 2017, ¶ 23,)

**c. homology between serotypes Ad2 and Ad5 and other human subgroups, in other mammals or in birds**

86. According to Dr. Curiel, research on Ad2 and Ad5 human adenovirus serotypes is not predictive for creating recombinant adenoviruses using the genome of non-Ad2/5 viruses (Ex 2017, ¶ 28).

87. Further according to Dr. Curiel,

> [a]denoviruses share similarities but these do not translate into predictable biological behaviors or structural organization. For example, ovine adenoviruses were and still are of interest for vectors for gene therapy, however, the structural organization of the genome does not parallel human Ad2 or Ad5. For example, the location of the MLP and associated tripartite leader sequence or VA RNA sequences were not discovered until well after 1994. Not until 1998 was it learned that ovine Ad contained a rearranged genome and a single promoter (in contrast to human Ad2 and Ad5). Exhibit 2016. Thus, one of skill in the art would not have been able to create and multiply defective ovine Ad derived from vectors based upon the limited instructions offered in the '225 application. [Ex 2017, ¶ 29.]

**d. providing complementing cell lines that enable propagation of multiply-deficient adenoviruses is unpredictable**

88. According to Dr. Curiel,

> [a] "[t]he successful production of a [sic] one complementing cell line, even for a single gene region, does not suggest that the same cell line will be useful for complementing any other deficient adenoviral gene region" (Ex 2017, ¶ 14-15).
>
> [b] For example, A549 cells but not Vero cells can be stably

transfected with E1 expression plasmids to produce an E1 complementing cell line (Ex 2020, ¶ bridging pp. 76-77).

[c] There are technical difficulties associated with the construction of cell lines (see, e.g., Weinberg et al. [Ex 2014], supra at 5383, which states "many segments of DNA do not transform cells, and there is no direct selection for cells that contain such DNA and that might support the growth of mutants in those regions of a viral genome"). Some adenovirus gene products function at levels in adenovirus replication that are toxic to the recipient cell (e.g., E2A-DBP (Klessig et al. [Ex 1004]). Such toxicity can confer upon cells having reduced expression of the gene a growth advantage as compared to a cell containing the deficient gene, resulting in an inability to obtain cell lines that contain the complementing gene and, hence, an inability to propagate adenoviruses deficient for that gene (Ex 1004 at 1354).

**E. Amount of direction or guidance presented**

89. Dr. Curiel also testified that

[a] [t]he '225 application does not describe or even suggest an approach for creating, for example, vectors with deficiencies in E2B, MLP-L1, the 13.5 kD gene, late genes (e.g., L1-L5), pIX, the ITRs or packaging sequences, or how to create cell lines capable of complementing deficiencies of all early and late gene regions sufficiently to produce the vectors as claimed (Ex 2017, ¶ 15).

90. Further according to Dr. Curiel, the Perricaudet '225 application (Ex 2002) "does not describe or provide any guidance for how to construct complementing cell lines using adenovirus sequences other than Ad2 and Ad5, even for 293 cells. Similarly, the application does not provide guidance or even suggest how to create complementing cell lines for adenoviruses other than those derived from human Ad2 and Ad5." [Ex 2017, ¶ 26.].

91. Rather, Perricaudet '225 (Ex 2002, p. 5, ll. 5-10) simply reads that, "[t]here are various adenovirus serotypes whose structure and properties vary somewhat. Nevertheless, these viruses exhibit a comparable genetic organization, and the

information described in the present application can be easily reproduced by persons skilled in the art for any type of adenovirus."

**F. Presence or absence of working examples**

There are several working examples presented in Perricaudet '225 (Ex 2002, pp. 15-29).

92. Examples 1 and 2 are said to disclose construction of vectors in which E4 is the only gene carried by the vector (id., pp. 15-18).

93. Example 3 is said to disclose a vector which carries only the E2 gene (id., pp. 18-20).

94. Example 4 is said to disclose construction of a ΔE1ΔE2A and/or ΔE4 adenoviral vector complementing cell line wherein "the recipient cell line for this virus construction is the triple complementing cell line 293/E4/E2A" (id., pp. 20-21).

95. Example 5 is said to disclose construction of an adenovirus which is defective in E1, E3 and E4 (id., pp. 21-26).

96. Example 6 is said to describe construction of an adenovirus whose genome is defective in E1, E3, L5 and E4 (id., pp. 26-29).

97. There is no working example of a replication-defective recombinant adenovirus with deletions of ΔE2B, and/or deletions of late genes (ΔL1-L5) in Perricaudet '225.

98. According to Dr. Curiel, no complementing cell line has ever been described that could complement for late genes or vectors deleted of the entire E2 region (Ex 2017, ¶ 20).

**G. Quantity of experimentation necessary**

Based on Dr. Curiel's testimony, it appears that the quantity of experimentation necessary to practice the full scope of Perricaudet claims 34 and 42 is undue in view of the high degree of difficulty and unpredictability in the field of the invention given the breadth of these claims.

**H. Gencell's opposition**

Gencell argues that the examples and methods disclosed in Perricaudet '225 (Ex 2002) provide a disclosure which enables one skilled in the art to practice the claimed invention without undue experimentation. With respect to toxicity issues, Gencell argues that even though a transcribed structural protein may be toxic to a host cell, after new particles are formed during infection, the cell undergoes lytic release of virions and the cell's response to toxic accumulation of late gene products becomes irrelevant. [Paper 61, p. 6.] Gencell provides no evidence to support these arguments.

Gencell further argues that the Perricaudet '225 specification (Ex 2002) clearly discloses the use of helper viruses to complement recombinant adenoviruses in Examples 1-3 and at p. 1, ll. 24-35. Thus, Gencell argues that at the time of filing, the practice of using helper viruses in propagation of adenoviral vectors was conventional and well known to one of skill in the art. [Paper 61, p. 6.] The '225 specification (Ex 2002, p. 11), indicates that "it is not necessary to have a competent cell line capable of complementing all the defective functions of the virus. Part of the functions is indeed complemented by the helper virus. This helper virus should itself be defective and the cell line carries *in trans* the functions necessary for its complementation."

Perricaudet '225 provides examples of the use of a helper virus, which incorporates into a plasmid and complements for large portions of DNA of the recombinant virus. These examples do not, however, address the use of a complementing cell line to supplement or supply multiple E2 gene deletions of the adenovirus and/or MLP functions opposite E2B.

In response to Wang's argument regarding deletions of the adenoviral genome below 25 Kd and vector instability, Gencell argues that the problem of instability relating to an over-deleted genome was not discovered until well after the filing date of Perricaudet '225 (Ex 2002). Thus, Gencell further argues that Perricaudet did not knowingly claim inherently unstable adenoviral vectors.

The 1997 Parks publication[19] (Ex 2010) is acknowledged but has not been considered part of the state of the prior art available at the time of filing of the Perricaudet '225 application (Ex 2002).

Gencell generally argues that the fact that the claims may encompass some inoperable embodiments does not necessarily invalidate them. Crown Operations Int'l, Ltd. v. Solution, Inc., 289 F.3d 1367, 1380, 62 USPQ2d 1917, 1925 (Fed. Cir. 2002); Atlas Powder Co. v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984). "[I]f the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid." EMI Group

[19] Parks et al. (Parks), "A Helper-Dependent System for Adenovirus Vector Production Helps Define a Lower Limit for Efficient DNA Packaging," Journal of Virology, Vol. 71, No. 4, pp. 3293-3298 (Ex 2010).

North America Inc. v. Cypress Semiconductor Corp., 60 USPQ2d 1423 (Fed. Cir. 2001); Atlas Powder Co., 750 F.2d at 1576-77, 224 USPQ at 414.

**I. Legal analysis**

While the level of skill in the art is high, the breadth of the claims (which is not limited to vectors reciting combinations of deletion of the gene functions of ΔE1ΔE4, ΔE1ΔE2 or ΔE2AΔE4) taken together with the limited amount of guidance and working examples in Perricaudet '225 (Ex 2002) weigh in favor of nonenablement. Undoubtedly, it is well within ordinary skill in the art to delete genetic material per se from any genome, e.g., using conventional restriction enzymes. However, given that the deleted genetic material must comprise one or more essential adenoviral gene functions and given the complexity of the adenoviral genome and life cycle, the skilled artisan must know not only what genetic material to delete, but also how to resupply the vector with the missing genetic information in the appropriate amount at the appropriate times in order to allow the vector to propagate.

Whether the overall organization of the adenoviral genome is conserved among serotypes of a species such that similar specific functions are similarly positioned, is a factor because the claims at issue are not limited to any particular species, subgroup or subgenus. Whether members of human species adenovirus subgroup C may have highly homologous DNA, is a factor because Gencell has not pointed us to evidence that the same is true for other human adenovirus subgroups. Moreover, the claims at issue are not limited to human adenoviruses. Perricaudet '225 (Ex 2002) gives little guidance regarding vectors with deletions in other than the E1, E2A and E4 regions.

Additionally, some genes direct more than a single gene function and Dr. Curiel has testified that Perricaudet '225 lacks sufficient disclosure to enable the skilled artisan to delete a single gene function, without deleting the remaining functions directed by that gene (FF 55). For example, in Dr. Curiel's opinion as one of ordinary skill in the art, Perricaudet '225 does not exemplify how to construct adenoviral vectors deficient in E2B, MLP, late genes L1-L5, protein IX (which overlaps with the E1B region), ITRs and packaging sequences (Ex 2017, ¶ 15).

In short, the prior art and Perricaudet '225 (Ex 2002) do not provide sufficient information of the location of replication-essential regions of the adenoviral genome commensurate in scope with the various species, serotypes, subgroups and subgenera of the adenovirus family to enable the skilled artisan to create replication-defective vectors and complementing cell lines therefor commensurate in scope with the breadth of the remaining Perricaudet claims, i.e., claims 19-27, 33-34 and 42, without undue experimentation.

Even assuming arguendo that one knew how to selectively ablate a desired essential gene function, the complementation problem remains. Use of complementing cell lines for singly-deficient adenoviral vectors was known, e.g., 293 cells supplied E1 gene function and W162 cells supplied E4 gene function. However, Dr. Curiel testified that there was no expectation of success of a unique vector or cell line based on the reported success of another (Ex 2017, ¶ 14-15).

In view of the above, the framework provided by the Perricaudet '225 specification is insufficient to enable the skilled artisan to make and use the full scope

of Perricaudet claims 34 and 42. Gencell has not persuaded us otherwise.

Based on the foregoing, Wang preliminary motion 3 is **granted** as to Perricaudet '225 claims 34 and 42, and otherwise **dismissed**.

## XVIII. WANG PRELIMINARY MOTION 2

Pursuant to 37 CFR § 1.602(a), Wang seeks judgment against Vigne as between junior party Vigne and senior party Perricaudet, both commonly assigned to Gencell (Paper 36). Gencell opposes (Paper 60); Wang replies (Paper 82).

According to 37 CFR 1.602(a), in relevant part, unless good cause is shown, "an interference shall not be declared or continued between (1) applications owned by a single party or (2) applications and an unexpired patent owned by a single party." Rule 602(a) is properly interpreted as applying to multi-party interference where all of involved applications or patents are not commonly owned, and as requiring election between two commonly held applications and/or patents unless good cause exists for both to continue in interference.

The purpose of the count is to determine what evidence is relevant to the issue of priority. Case v. CPC Int'l, Inc. , 730 F.2d 745, 749, 221 USPQ 196, 199 (Fed. Cir.) (citation omitted), cert. denied , 469 U.S. 872 (1984). In Barton v. Adang, 162 F.3d 1140, 49 USPQ2d 1128 (Fed. Cir. 1998), the board required the junior party, Monsanto to elect between its two commonly owned applications prior to preliminary motions and setting of final counts in the interference. At the time that Monsanto was forced to make an election between the Barton et al. and the Fischhoff et al. applications, it was not clear what the content of the final count would be or what

proofs on dates of conception and reduction to practice Adang et al. would seek to establish. At this stage of the proceedings, Monsanto could not determine which application, either Barton et al. or Fischhoff et al., would be the best evidence to establish priority. The Federal Circuit held that Monsanto had shown "good cause" to continue the interference on both its applications until the preliminary motions to finalize the count are decided by the Board and discovery is complete, i.e., requiring Monsanto to elect between Barton et al. and Fischhoff et al. was premature. Similarly, here, election by Gencell between the Vigne patent and the Perricaudet application prior to finalizing the counts in this interference would be premature.

Therefore, as a result of this decision on motions, the administering APJ will issue separate orders (a) redeclaring the interference with "finalized" counts and (b) ordering Gencell to show good cause why it should not be required to elect between commonly owned Vigne patent '175 and Perricaudet application '225 as to the "finalized" counts pursuant to 37 CFR § 1.602(a).

Based on the foregoing, Wang preliminary motion 2 is **dismissed** as premature and subject to further appropriate action by the APJ as discussed above.

## XIX. GENCELL MISCELLANEOUS MOTION 2

Gencell moves to suppress Wang Exhibit 2022, the sworn testimony of Gary Ketner, Ph.D., in Interference 104,825, "under 37 CFR § 1.671 et seq." (Paper 95).

Gencell miscellaneous motion 2 is moot insofar as we have not relied on the testimony of Gary Ketner, Ph.D. (Ex 2022) in this interference.

Therefore, Gencell miscellaneous motion 2 is **dismissed**.

## XX. ORDER

Therefore, upon consideration of the record, and for the reasons given, it is:

ORDERED that Gencell preliminary motion 2 is **granted**, there is no interference-in-fact between Wang claim 48 and Perricaudet claims 19-20, 23 and 25-27, corresponding to Count 2.

FURTHER ORDERED that Gencell preliminary motion 3 is **denied**.

FURTHER ORDERED that Gencell preliminary motion 6 is **denied** as to Perricaudet claims 21, 22 and 33 and otherwise **dismissed**.

FURTHER ORDERED that Wang preliminary motion 1 is

(a) **granted** with respect to Count 1, there is no interference-in-fact between Wang claims 56 and 58 and Perricaudet claims 1-3, 9, 12-18, 28, 30, 35 and 40-41, the only claims corresponding to Count 1;

(b) **granted** with respect to Count 2, there is no interference-in-fact between Wang claim 48 and Perricaudet claims 19-20, 23 and 25-27, the only claims corresponding to Count 2;

(c) **granted** with respect to Perricaudet claims 1-3, 9, 12-18, 28, 30 and 40-41, but **otherwise denied**, there is an interference-in-fact between Wang claims 37-38, 46-47, 52, 54 and 56 and Perricaudet claim 34, which correspond to Count 3;[20]

(d) **granted** with respect to Count 4, there is no interference-in-fact between Wang claims 39-44 and 57 and Perricaudet claims 19-23, 25, 27 and 33;[21]

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[20] Vigne claim 33 also corresponds to Count 3.

[21] Vigne claims 1-6, 11-16, 20-21 and 23-25 also correspond to Count 4.

(e) **denied** as to Count 5, there is an interference-in-fact between Wang claims 37, 46, 54 and 56 and Perricaudet claim 42, the only claims corresponding to Count 5; and

(f) **granted** as to Count 6, there is no interference-in-fact between Wang claims 48 and 57 and Perricaudet claim 42, the only claims corresponding to Count 6.

FURTHER ORDERED that Gencell preliminary motion 4 is **denied**.

FURTHER ORDERED that Gencell preliminary motion 7 is **granted**, subject to the APJ taking further appropriate action.

FURTHER ORDERED that Gencell preliminary motion 9 is **denied**.

FURTHER ORDERED that Gencell preliminary motions 10 through 13 and 15 are **dismissed** as moot.

FURTHER ORDERED that Gencell preliminary motion 14 is **denied**.

FURTHER ORDERED that Wang preliminary motion 4 is **granted**. Perricaudet claim 42 is unpatentable for failure to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

FURTHER ORDERED that Wang preliminary motion 3 is **granted** as to Perricaudet claims 34 and 42 and otherwise **dismissed**. Perricaudet claims 34 and 42 are unpatentable under 35 U.S.C. § 112, first paragraph, as not enabled throughout their scope.

FURTHER ORDERED that Wang preliminary motion 2 is **dismissed** without prejudice to the APJ taking further appropriate action.

FURTHER ORDERED that Gencell miscellaneous motion 2 is **dismissed**.

FURTHER ORDERED that a copy of this decision (Paper 116) be given a paper

number and entered into the administrative record of Vigne/Gencell Patent 6,127,175; Wang application 08/333,680 and Perricaudet/Gencell application 08/397,225.

RICHARD TORCZON
Administrative Patent Judge

CAROL A. SPIEGEL
Administrative Patent Judge

DEMETRA J. MILLS
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